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General Medicine

Relation of Pituitary-Adrenal Function to the Rheumatic Diseases — Grier, George Smith, III — *Virginia Medical Monthly*, 77: 66 (February) 1950.

The theory and application of Seyle's General Adaptation Syndrome are presented and the physiologic effects of the adrenal cortical hormones are discussed.

"The syndrome is characterized by a number of morphologic and functional changes. Among the most prominent of these are enlargement of the adrenal cortex with increased corticoid hormone secretion, involution of the thymus and other lymphatic organs, gastrointestinal ulcers, and certain metabolic changes and variations in the resistance of the organism. If an individual is continuously exposed to stress, the resulting General Adaptation Syndrome evolves in three distinct stages.

"Stage 1.—Alarm reaction—sum of all systemic reactions due to sudden exposure to stress to which the organism is not adapted. Some of these phenomena are only passive and represent signs of damage or shock such as hypothermia, hypotension, hypochloremia, hemoconcentration, increased capillary permeability, and depression of the central nervous system; others are manifestations of active defense against shock such as adrenal cortical enlargement, increased corticotropin and corticoid production, hyperchloremia, etc. Usually the alarm reaction evolves in two distinct phases, the phenomena of shock being followed by those of countershock.

"Stage 2.—Stage of resistance—sum of all nonspecific systemic reactions elicited by prolonged exposure to stress and strain to which the organism has become adapted. It is characterized by an increased resistance to the particular agent to which the body has been exposed and this is usually accompanied by a marked decreased resistance to other types of stress. Essential hypertension is said to fit into this stage.

"Stage 3.—Stage of exhaustion—represents the sum of all nonspecific systemic reactions which ultimately develop as the result of very prolonged exposure to stress or strain to which adaptation has been developed but could no longer be maintained. In this stage there is atrophy and hypofunction of the adrenal cortex.

"The adrenal cortex has three main functional types of hormones or corticoids:

"1. Mineralocorticoids control inorganic metabolism of Na-Cl-K-H_2O. This corticoid causes urinary retention of sodium and chloride and increased excretion of potassium. The most potent electrolyte-regulating adrenal steroid is 11-desoxycorticosterone which has been synthesized and called DOCA. There is no direct way of measuring this corticoid in the blood or urine.

"2. Glucocorticoids 'S' or sugar hormones—control organic metabolism. This hormone causes increased blood sugar level, increased liver glycogen stores, increased conversion of protein to carbohydrate (gluconeogenesis), increased mobilization and utilization of fat, increased renal clearance of uric acid in normal and gouty patients, lysis of lymphoid tissue, and marked decrease in circulatory eosinophils. Its activity is directly measured by the 11-oxycorticosteroids in the urine."

"3. Androgens or sex hormones ('N' hormones) cause retention of nitrogen and protein within the body and control secondary sex characteristics such as hair, weight, voice, size of clitoris. Activity is measured by the presence of the 17-ketosteroids in the urine. In the male two thirds of the androgens come from the adrenal cortex and one third from the testes; in the female all the hormone comes from the adrenal cortex.

"The adrenal cortex contains lifemaintaining and lifesaving substances which are increased in the alarm reaction and markedly decreased in the stage of exhaustion.

"The theory is that the stress or strain stimulates the hypothalamus, which in turn stimulates the anterior pituitary to liberate adrenocorticotropic hormone or ACTH, which then stimulates or causes hyperfunction of the adrenal cortex and, if the stimulation is prolonged, the adrenal cortex becomes exhausted and results in hypofunction."

One can give ACTH to a normal person and show hyperfunction of adrenal cortex by the presence of oliguria, increased specific gravity of the urine, elevated blood sugar, and impaired glucose tolerance, retention of sodium, excretion of potassium and uric acid, high levels of 11-oxycorticosteroids and 17-ketosteroids in the urine, and fall in circulating eosinophils.

"Prolonged use of ACTH may cause exhaustion of the adrenal cortical function and reversal of the above findings. The fall in circulating eosinophils affords the most sensitive clinical indicator of adrenal cortical activity."

"It was found that small doses of epinephrine at six hour intervals resulted in moderate stimulation of the adrenal cortex as shown by fall in eosinophils and urine steroid excretion.

"Adrenal cortical hyperfunction or corticoid stimulation causes disintegration of lymphocytes with liberation of antibodies from this lymphatic tissue and may play an important role in immunity and allergy since lymphatic tissues store antibody globulins.

"In allergic states such as asthma, periarteritis nodosa, hay fever, etc., there is an increase in eosinophils which is also seen in exhausted state of the adaptation syndrome.

"During the alarm reaction, as following surgical procedures, the bleeding and coagulation times are decreased, platelets increased, and fibrin formation accelerated, which may account for the frequency of phlebothrombosis in postoperative cases.

"Continuous exposure to certain types of stress or strain such as cold, fright, etc., in rats on high sodium and protein diet and sensitized by unilateral nephrectomy, causes hypertension, periarteritis, hyalinization and inflammation of the renal arterioles and formation of fibrous nodules in the heart which resemble the Aschoff nodules of rheumatic fever. In these animals the adrenal cortex is found to be hypertrophied and the same changes can be produced by ACTH or DOCA. Perhaps in these conditions there is an imbalance of the mineralocorticoid which takes place under certain conditions of stress, strain, diet and genetic predisposition. The same changes in humans may take place under certain conditions of stress and strain."

Gastrointestinal ulcers are frequently seen during the shock phase of the alarm reaction as in burns (Curling's ulcer), or in intense emotional excitement.

Adaptation to one's surroundings is one of the most important physiologic reactions in life.

"Since the previously so important infectious diseases are now largely under control, thanks to the progress in research on antibiotics, even greater stress will have to be placed in the future upon the diseases of adaptation and the wear and tear maladies of aging."

"Increased hyaluronidase levels in the serum and hypofunctioning of the adrenal cortex may be the pathologic physiology common to the collagen diseases."

"Dramatic remissions of rheumatoid arthritis during pregnancy, jaundice, anesthesia, surgical operations, and other conditions of stress led Hench to believe that an adrenal hormone may be responsible for the improvement since all these conditions stimulate the adrenal cortex in the alarm reaction."

Compound E or 17-hydroxy-11-dehydrocorticosterone was used on 14 patients, all of whom had severe or moderately severe rheumatoid arthritis. "All patients had 'marked' improvement in a few days on daily injections of 100 mg. of Compound E or Cortisone and relapses occurred in a short time when the drug was discontinued. The improvement was not only subjective, but marked decrease in the sedimentation rate, increase in hemoglobin, RBC, weight, appetite, euphoria, and serum proteins occurred. First to improve was the muscular and articular stiffness in 48 hours, then the articular swelling

and tenderness subsided. Doses less than 100 mg. daily proved to be insufficient and must be given continuously or a relapse will likely occur.

"Identical results are seen with ACTH in doses of 40 mg. daily. The use of ACTH simply stimulates the adrenal cortex and the patient manufactures his own endogenous Compound E or Cortisone."

"The use of Cortisone and ACTH in acute rheumatic fever has proved to be just as dramatic as in rheumatoid arthritis. Not only has there been prompt disappearance of fever, tachycardia, and polyarthritis in a few days, but the sedimentation rate and P-R interval have become normal within two weeks. Much time must elapse before any definite conclusions can be drawn as to the effect of Compound E on rheumatic heart disease, but cardiac muscles and fibrous valves are not very different histologically from skeletal muscles and fibrous tissue." The helpful effect which Compound E has upon the muscles and fibrous tissues of rheumatoid patients, an effect which appears to be more than one of simple analgesia, permits one to hope that cardiac muscles and valves may respond similarly. The glucocorticoids cause a marked increase in excretion of uric acid in both gouty and normal persons. With this in mind, one writer used ACTH in patients with gout which produced a large increase in urinary uric acid and a prompt fall in the serum uric acid. "The clinical improvement was striking and rapid, much more so than with salicylates.

"Disseminated lupus erythematosus, periarteritis nodosa and dementia praecox have also been found to respond to Cortisone and ACTH." The dangers of continued ACTH or Compound E Acetate treatment are essentially the undesirable side effects associated with prolonged high level of adrenal steroids, and these effects are not known yet.

"The beneficial effect of these substances in the rheumatic diseases is a great advance in therapy. The use of adrenal cortical steroids and adrenal cortical stimulants will do much to further research in the diseases of adaptation which include the collagen diseases, nephrosclerosis and hypertension."

Effects of Delta 5 Pregnenolone in Rheumatoid Arthritis — DAVISON, ROLAND, KOETS, PETER, SNOW, WILLARD G. AND GABRIELSON, LYMAN G.— *Archives of Internal Medicine*, 85: 365 (March) 1950.

"Intramuscular injections of pregnenolone have been given to 30 patients. Twelve of these patients, 8 males and 4 females, have typical ankylosing spondylarthritis; 13 patients have rheumatoid arthritis; 1 has rheumatoid arthritis with spondylarthritis and degenerative joint disease; 1, rheumatoid arthritis complicated by glomerulonephritis (this case may be early disseminated lupus), and 1, rheumatoid arthritis with psoriasis."

"For the initial experiments pregnenolone acetate in sesame oil, 50 mg. per ml., in 10 ml. rubber-capped vials, was supplied. Subsequently an aqueous suspension of crystalline pregnenolone (100 mg. per ml.) was tried. Use of this material was discontinued because injection of it was difficult. More recently pregnenolone acetate in 80 per cent sesame oil and 20 per cent benzyl benzoate (50 mg. per ml.) and an aqueous suspension of pregnenolone (50 mg. per ml.) have been used.

"All the patients were hospitalized for initial studies, and some were hospitalized for the entire period of investigation. A few were given pregnenolone as ambulatory outpatients. . . . None of the patients were on strict dietary control, and balance studies were not made."

"The patients were told that the injections were a new treatment which might help or might not. Placebos were given without knowledge of the patients when the change was made, nor did they know when pregnenolone was again given them. Dosage schedules have been varied from 50 to 300 mg. a day. When pregnenolone acetate was used, 100 mg. was given at a single injection, and when the dosage was increased to 200 mg. two injections were given each day. Pregnenolone aqueous suspension in the later experiments has been given in two daily injections of 150 mg. each.

"Warming of the vials has been necessary to secure solution of the crystals when the acetate in oil was used; otherwise, the oil preparation shows undissolved crystals.

The injection of the cold material occasionally has caused pain in women; such pain did not occur in the males. When the vials were warmed and the material then injected, no pain occurred. When aqueous suspension was given, some of the patients experienced a prickling or stinging sensation at the site of injection for 5 to 10 minutes after injection."

In most cases, the pattern of response was the same. In spondylarthritis, ketosteroid excretion was reduced in a few days, accompanied with increased mobility of the spine in cases in which fixation was due to spasm, not ankylosis. "Pain and spasm were greatly diminished, and in patients with diminished chest expansion it increased. In those patients having rheumatoid arthritis involving joints of the extremities, usually within a week and sometimes within three or four days there was relief of stiffness and pain, great improvement in muscle strength and loss of fatigue, which was replaced by a feeling of well-being.

"Appetite was frequently but not invariably improved. In those patients with anemia the blood picture improved rapidly. Reduction in joint swelling, particularly in those cases with large joint effusions, came more slowly. Reduction in sedimentation rates did not parallel clinical improvement but came later.

"No evidences of toxicity have been observed from prolonged administration of pregnenolone. There has been no elevation of the fasting blood sugar and no edema. There has been no effect on the menstrual cycle, the duration of menstruation or its character in any of the women who have received it. Pregnenolone is a known stimulant to spermatogenesis; though sperm counts have not been made, none of the men has had diminished potency. One man who had lost sexual potency recovered it while he was under treatment, probably as a result of control of the disease and improvement in general strength."

Euphoria is not seen in patients receiving pregnenolone. "One patient did become exhilarated and had difficulty sleeping on a daily dosage of 300 mg. of the pregnenolone aqueous suspension.

"When use of pregnenolone is discontinued after short term administration, symptoms and signs of active arthritis recur in a few days. One patient who received pregnenolone daily for 37 days and then was given 100 mg. of pregnenolone acetate every two days for two months continued to show no evidence of arthritis; five days after discontinuance of its use pain and joint swelling recurred."

Comment on additional patients who have received pregnenolone deserve mention. "There were 4 men and 2 women with spondylarthritis. Two of the men who had great clinical improvement from 100 mg. of pregnenolone daily for three and four weeks respectively were lost by transfer to other hospitals. One man with complete ankylosis of the spine and little residual active disease showed no perceptible change from 50 mg. of pregnenolone acetate daily over a two week period and refused further trial of the steroid. One woman with ankylosing spondylarthritis had a complicating psychosis. She appeared greatly improved in two weeks, but evaluation was unsatisfactory because of the psychosis. One woman with psoriasis and rheumatoid arthritis failed to show symptomatic or objective improvement from daily injection of 100 mg. doses of aqueous suspension for two weeks, and refused further injections.

"One 34 year old man with severe gouty arthritis was given 200 mg. of pregnenolone acetate for six and one-half days without benefit. The same patient was given 100 mg. of pituitary adrenocorticotropic hormone (ACTH) divided into six doses at six hour intervals, also without symptomatic or objective improvement, although the ACTH increased excretion of uric acid.

"One young woman with a diagnosis of disseminated lupus was given 300 mg. of pregnenolone aqueous suspension daily for two weeks. The articular symptoms were slightly improved and the swelling was reduced, but she was so greatly emaciated and had so little muscle into which the material could be injected that injections were discontinued.

"One 54 year old white woman has had long-continuing active rheumatoid arthritis resulting in much destruction and deformity of joints and known allergy to many drugs. Her obese buttocks made injections difficult, and many of them failed to de-

posit the oil solution in the muscle, resulting in large, hard, painful nodules necessitating discontinuance of treatment."

"Though the intramuscular injection of pregnenolone appears to bring about remission of rheumatoid arthritis within a short time, its action in some cases is delayed as long as three or four weeks. . . . Patients with spondylarthritis with low urinary 17-ketosteroid excretion appear to respond more slowly, and 2 spondylarthritic patients who received what appeared to represent adequate dosage of pregnenolone failed to respond.

"The recurrence of symptoms and objective evidence of activity within days after the hormone is discontinued appears to be good evidence that the steroid is responsible for the observed effects. . . . The results of injection of aqueous suspension of crystalline pregnenolone are much less effective than pregnenolone acetate in oil."

"Pregnenolone appears to be less rapidly effective than either 17-hydroxy-11-dehydrocorticosterone or the pituitary adrenocorticotropic hormone (ACTH). Unlike them, it appears to be free of the toxic effects which result from their administration over long periods."

A New Method for Determination of the Blood Coagulation Time — MENGHINI, GIORGIO — *Schweizerische medizinische Wochenschrift*, 80: 139 (February 11) 1950.

Difficulties in blood coagulation time determinations are encountered in actual practice which cannot easily be overcome, as indicated by the large number of methods in use. The indirect methods in which the blood is first made incoagulable and then the anticoagulant is again removed do not seem to furnish accurately the coagulation time of the blood in its original condition, and as none of the more or less complicated and ingenious methods suggested are completely satisfactory most authors returned to the simple test tube determination with the method of Lee and White which furnishes clinically useful results although the reading of the result involves a considerable subjective factor.

The author's method uses determination in the test tube but differs from other methods by its simplicity, by the minimalization of the subjective error in reading of the results and by the fact that the blood is not subjected to any agitation from the moment it is placed into the test tube until complete coagulation.

All glass utensils used for the determination must be prepared scrupulously; they must be kept for a protracted period in a sulfochromic mixture, then lavaged in abundant running water and subsequently in distilled water, and finally dried at room temperature. For a complete accurate determination 30 test tubes of 10 cm. height and 1.0 cm. inner diameter, two 5 cc. pipets with a 0.1 cc. graduation, and a glass syringe of 10 cc. are required, but for clinical determinations 10 to 12 test tubes are sufficient. Needles which are not too thin should be used for the venipuncture and they should always be of the same size; needle and syringe must be sterilized dry. With doubly distilled water and absolutely pure substances, a 0.65 per cent sodium chloride and a 4 per cent tribasic sodium citrate solution are prepared, and immediately before use 100 cc. of the former and 1 cc. of the latter are mixed. About 10 cc. of blood is taken with as little stasis as possible from a vein of the elbow region, and 0.3 cc. of blood is placed into each of the 30 test tubes with a pipet; the test tubes dip about 1 cm. into a water bath of 25° C. Three minutes from the beginning of the withdrawal of blood with the second pipet 4 cc. of the above mentioned fluid is put into the first tube and rapid mixture is produced, avoiding foam formation. At intervals of 30 seconds the same procedure is repeated with the other test tubes so that each tube receives the diluting solution within an exactly determined period of time after withdrawal of the blood.

Reading of the result is easy as the intense dilution of the blood permits visualization of the fibrin threads and larger clots which otherwise remain unnoticed in the cloudy thick mass of undiluted blood. The first tubes show a completely homogeneous content; approximately from the third to the seventh tube delicate fibrin threads appear, and in subsequent ones the fibrin particles become more numerous and larger and show a tendency to unite into a nonhomogeneous mass until at a

certain moment a well delimited clot is encountered which mirrors the rounded bottom of the test tube. Furthermore, as soon as blood coagulation is complete the diluting fluid which had shown a vividly red color before because of the large number of erythrocytes not yet included in the clot will suddenly turn almost colorless; this peculiarity permits one to recognize immediately the test tube corresponding to complete coagulation and therefore the corresponding time interval. When coagulation is complete fibrinogen is virtually completely transformed into fibrin while in incomplete coagulation this transformation is only partial; therefore, in the test tubes which received the diluting solution before complete coagulation a certain amount of fibrinogen will go into solution. Theoretically, this fibrinogen should clot after a certain period of time in all tubes in which coagulation had started and thrombin had formed even if only in a small quantity, but actually this does not always occur, perhaps because of the excessive dilution of the thrombin and also because the thrombin is neutralized before it can become effective. However, if after termination of the first reading 2 to 3 drops of thrombin or more simply 0.2 mol calcium chloride solution are added to each test tube and the mixture is left to stand at room temperature, or preferably at 37° C. for 60 minutes, the entire fibrinogen in the tubes with incomplete coagulation will clot. In this manner the accuracy of the data of the first reading can be checked; if the data are accurate complete coagulation of the entire mixture with formation of a long and progressively retracting clot will occur up to the test tube preceding the one with complete coagulation.

In clinical determinations in which only appearance of the first fibrin threads and complete coagulation is to be determined only 10 to 12 test tubes are required and intervals of 1 minute may be used between the first tubes, until the first fibrin particles appear, usually between the second and fourth tube. Then an interval equal to that between blood withdrawal and appearance of the first fibrin particles may be made, and from then on the intervals are regulated depending on aspect and size of the clots present; when it can be assumed that coagulation has advanced far intervals of 30 seconds are used, and otherwise intervals of 1 to 2 minutes.

If a probably markedly lengthened coagulation time is to be determined the intervals between the first dilutions may be 2 to 5 and even 10 minutes. On the basis of a large experience the author states that the first fibrin particles appear after an average of 4 to 6 minutes while coagulation becomes complete after 10 to 15 minutes.

The most original and most advantageous aspect of this method concerns the fact that the most important phase of blood coagulation; namely, the transformation of soluble fibrinogen into insoluble fibrin, can be followed up in its course and that the stages of this process are fixed so that reading is still afforded after coagulation is completed. The control of the presence of residual fibrinogen dissolved in the diluting fluid affords a conclusive evaluation of the moment of complete coagulation as it discloses a possible incompleted coagulation.

The Effect of Streptomycin upon the Pathology of Tuberculous Meningitis — WINTER, WILLIAM J. — *American Review of Tuberculosis*, 61: 171 (February) 1950.

"Twelve fatal cases of streptomycin-treated tuberculous meningitis were studied histologically with emphasis upon the pathological changes occurring in the leptomeninges, meningeal arteries, brain substance, and ependymal lining of the ventricles."

"The cases fell into three groups: first, the acute meningitis in which death occurred within two months without evidence of clinical improvement; second, subacute disease in which the patient lived three to four months with short intervals of improvement; and third, chronic disease in which there had been good clinical remissions for several months."

"Streptomycin induces a definite reparative process in tuberculous meningitis, as shown by the prolongation of life and the pathological changes observed in these fatal cases. These apparently occur as follows:

"The exudate in the subarachnoid space undergoes progressive organization. There

is early dissolution of much of the fibrin and replacement by actively proliferating fibroblasts and chronic inflammatory cells. The foci of necrosis tend to be either encapsulated or partially infiltrated by fibroblasts.

"The acute tuberculous arteritis, commonly involving the vessels in the circle of Willis and proximal branches of the middle cerebral arteries, rapidly is transformed into a proliferative endarterial reaction causing severe stenosis or occlusion of the vessels.

"Multiple ischemic softenings, which are consistent in the basal ganglions and internal capsule, result from the endarteritis, and are a common cause of neurological sequelae.

"Tuberculous ependymitis may resolve with the formation of small subependymal tubercles and well marked subependymal gliosis. Persistent granularity of the ependymal lining in a chronic case may be due to gliosis with the inward projection of numerous small glial tufts."

"The outstanding complications of streptomycin-treated tuberculous meningitis are communicating hydrocephalus and multiple ischemic softenings of the brain.

"Spinal block may develop due to extensive fibrous organization of the meningeal exudate in the vicinity of the site of intrathecal injections of the streptomycin."

"It is readily apparent that streptomycin treatment of tuberculous meningitis has been only the opening page for the effective treatment and cure of the disease. It is not yet the answer, but it has made the problems of treatment more clearly apparent."

Specific Therapy for Tuberculous Meningitis — BUNN, PAUL A. — *American Review of Tuberculosis*, 61: 263 (February) 1950.

"Streptomycin is the most effective tuberculostatic agent available, and it must remain the basic ingredient of any therapeutic regimen designed to treat tuberculous meningitis. Toxicity to it can be entirely ignored in the treatment of meningeal tuberculosis for no single toxic event or combination of them is as serious as the inevitable outcome of the disease without antimicrobial therapy. There is no contraindication to long term administration of streptomycin, courses of six months being feasible, even practicable. Other tuberculostatic materials, including any one of a number of sulfones, and paraamino salicylic acid have been added as adjuvant agents to streptomycin. It is not proved that a single one or combination of these has enhanced the total tuberculostatic effect of streptomycin alone, but it is most assuredly true that without streptomycin the use of any or all cannot be expected to alter significantly the outcome of tuberculous meningitis. It remains then for streptomycin to be employed wisely.

"Despite the fact that streptomycin is the common denominator in all successfully managed cases, there are certain discrepancies in the reported results which require comment. Among the unexplained facts are the differences in the case fatality rates observed in the various reported series of children with tuberculous meningitis. . . . These marked differences in fatality rates may possibly be due to the addition of a sulfone. . . . On the other hand, efficacy of treatment in adults has not been enhanced by the addition of either promin or paraamino salicylic acid. Similarly, initial, though small, cooperative and controlled studies under the auspices of the Public Health Service have failed to demonstrate significant improvement in the outcome of children treated with streptomycin and a sulfone over those treated with streptomycin alone. The discrepancy (15 to 30 per cent versus 50 to 66 per cent) remains unexplained and further observations must be recorded before the role of sulfones can be assayed accurately.

"It is possible that significant difference exists between the disease in children and in adults, a difference not appreciated prior to the use of streptomycin. That this is so is evident when results of antibacterial therapy in each group are studied. Figures for mortality in children range from 15 to 66 per cent. The variation in adults ranges from 50 to 90 per cent. These are statistically sound figures which indicate that survival occurs more often in children than in adults. The difference may be due to the method of administering streptomycin, to the particular therapeutic regimens utilized, or to the adjuvant use of sulfones. Most pediatricians have given relatively

large doses of streptomycin, often in excess of 100 mg. per Kg. body weight daily intramuscularly, and 100 mg. intrathecally. This fact may be of some consequence. Save for the first few cases in the Veterans Administration series, the usual daily intramuscular dose for adults has been from 2 to 3 Gm. (25 to 50 mg. per Kg. body weight). Prior to disclaiming the efficacy of large daily intramuscular and intrathecal doses, careful observations in a series of adults receiving from 6 to 8 Gm. daily appear to be in order.

"Irrespective of advantages possibly gained by excessive dosage of streptomycin, there still appears to be a difference in the disease according to age grouping. Three possible explanations of this unexpected phenomenon are offered, all speculative yet important perhaps, in further understanding of the problem for the therapeutist.

"Tuberculous meningitis in children is, in the majority of instances, closely related to the onset of primary tuberculosis, pulmonary or elsewhere. In the adult, meningitis usually develops in association with acute generalized hematogenous tuberculosis. It is conceivable that the central nervous system metastases from an active, or even subsiding, primary focus are less numerous than occur as a consequence of the acute, generalized hematogenous type of tuberculosis. Presumably an antibacterial agent can more effectively control a less than overwhelming tuberculosepsis and localized collections of few tubercle bacilli than the situation which usually obtains in the adult who develops tuberculous meningitis following dissemination of great numbers of organisms. It is also possible, in the attempt to explain the difference between childhood and adult meningitis, that immune body response or other host defense mechanisms are more rapidly mobilized and are more effectual in controlling a primary infection, when supported by proper antimicrobial materials, than they are in the individual afflicted with a chronic illness. It is assuredly true that, without extraordinary activity on the part of the host, streptomycin or any other tuberculostatic agent will not alone, or in combination, achieve eradication of a tuberculous infection in the brain or elsewhere. Ordinarily, the extensiveness of the primary focus is also far less of a problem of repair to the host than a chronic process in bone or lung of the adult—lesions associated with a greater amount of tissue destruction and fibrosis. In any event, the adult, because of ineffectual body defenses or a sudden spread of overwhelming numbers of organisms, or possibly because the pathologic process cannot completely reverse, does not respond as well to therapy for tuberculous meningitis as does the child.

"There is yet another unexplained fact that deserves comment. The discrepancy in the reported figures concerning the mortality rate of the disease solely in adults also varies considerably. This may be due to variations in treatment techniques. Modifications of treatment regimens are as numerous as the authors reporting them. It is impossible, indeed, to find a single commonly used schedule, albeit, principles of therapy are remarkably similar."

"There is unanimity of opinion that the presence of acute generalized hematogenous (miliary) tuberculosis with meningitis reduces significantly the chance for survival. . . . There is no apparent explanation for this observation except that the patient, young or old, must fight two otherwise fatal complications. The very fact that both complications develop, irrespective of focus from which the dissemination occurs, indicates that immunity has been overwhelmed and, presumably, that multiple foci of disease produce almost insurmountable handicaps for the tuberculostatic ability of streptomycin. It must be emphasized that from 50 to 67 per cent of all adults with miliary tuberculosis will sooner or later develop meningitis. It is apparent that, for preventive reasons, patients under therapy for miliary disease should be subjected to routine periodic cerebrospinal fluid examinations so that the advent of meningitis can be promptly diagnosed and proper changes in the therapeutic program instituted.

"In order to draw together other individual advantages of each regimen, a description of what appears to be an ideal treatment outline is offered below."

"It is advisable to administer at least 2 to 3 Gm. of streptomycin or dihydrostreptomycin intramuscularly in two to four divided doses each day for adults, and 100

mg. per Kg. per day for children who weigh less than 20 Kg. It is not possible to state that 6 to 8 Gm. daily may be indicated. In the writer's opinion, doses larger than 2 to 3 Gm. daily probably do not offer increased antibacterial protection to the patient. Nevertheless, as present information indicates that survival rates are best in those series in which the largest amounts of streptomycin are administered, it is apparent that further studies in the problem of daily dosage must be made.

"In the opinion of most authorities, it is essential to augment intramuscular therapy with direct additions intermittently of extra amounts of streptomycin intrathecally. Fifty to 100 mg. to adults and 2 mg. per Kg. per injection to children weighing less than 25 Kg. are needed. When these amounts are injected slowly, serious untoward irritative reactions are reduced to a reasonable minimum.

"No precise definition of how long streptomycin should be administered can be proffered. At least 120 days' total treatment by parenteral administration seems necessary; less is probably insufficient, and more is not contraindicated. Certainly, treatment periods of six months are worth the expense and trouble if prolonged clinical remissions are not obtained sooner. From the reported experience, at least 40 separate intrathecal injections are necessary and it is recommended that there be daily injections for at least six weeks. Thereafter this minimal therapy may have to be extended if clinical signs and cerebrospinal fluid components have not properly subsided. Certain clinical and laboratory criteria can be utilized to aid partially in the decision to continue or to discontinue intrathecal therapy. Determinations of the sugar and chloride content of the cerebrospinal fluid should be normal, the cell count should be at a steady low level; i.e., below 80 cells per cu. mm. and the value for total protein should be stabilized below 75 mg. per 100 cc. For as long as streptomycin is given intrathecally, values of the latter two elements may not return to normal because of the initiative action of streptomycin. All clinical evidence of central nervous system infection should have disappeared before cessation of therapy is advisable. Following cessation, retreatment is indicated if the cerebrospinal fluid cell count does not return rather promptly to normal, if the protein does not fall to normal over a period of a few weeks, and whenever clinical infectious relapse becomes obvious.

"In the presence of cerebrospinal block, interrupting the spinal flow of cerebrospinal fluid, intracisternal injections of streptomycin are feasible and may be necessary. The same schedule of injections obtains as that suggested above. If a block to the system occurs at a higher level, a surgical procedure (for example, removing ventricular fluid at intervals through surgically established frontal burr holes or short circuiting the ventricular system) may be warranted.

"These rather arbitrary definitions of treatment with streptomycin are not ideal but it appears that they represent basic requirements. Although the addition of adjuvant drugs (paraamino salicylic acid, promin, promizole) may not improve the results, it seems logical to add one or more to the regimen until the question is settled. At least 10 Gm. of paraamino salicylic acid daily, given orally for as long as six months, are probably needed, and blood levels of promin should be maintained at a level of 2 mg. per 100 cc. Promin can be given orally or parenterally by vein. Untoward side reactions are observed more frequently by the former route. Apparently the material is broken down in the small intestine and the more toxic parent substance, 4-4-diaminodiphenyl sulfone, formed before absorption. It is because of this that promin by vein is more desirable. Promizole by mouth has some tuberculostatic activity and is considerably less toxic than promin though given in larger amounts. Although a derivative of 4-4-diaminodiphenyl sulfone, it becomes conjugated in the gastrointestinal tract and is absorbed as a soluble material having antibacterial activity without the associated and expected toxicity of the parent substance.

"As the present mortality rate remains high and as all too often a 'successful' end result may be a person with serious and irreversible brain damage, some rearrangement of, or addition to, the schedules in the hope of possibly altering the outcome seems appropriate. Study of the pathology of the disease gives two enlight-

ening facts. Presumably streptomycin keeps the infecting organism in a state of bacteriostasis. The majority of deaths are not, therefore, the result of overwhelming proliferation of the bacteria or its toxins. Deaths occur for the most part because of the development of a degenerative hydrocephalus and/or widespread cerebral arteritis and thrombosis which is responsible for severe encephalitis. The British have recently reported the use of streptokinase, added to intrathecally administered streptomycin. As this material has the ability to dissolve fibrin, which when deposited about the brain stem generally results in obstructive hydrocephalus, combined therapy with streptomycin and streptokinase may very well solve, partially at least, the problems of hydrocephalus. Recently the Army has added heparin to the regimen in use, in the hope that continued cerebral arteritis may be held to a minimum, thus preventing brain damage. Both measures deserve immediate and careful study.

"One feature of the antagonism between the tubercle bacillus and streptomycin deserves comment. Temporary but impressive clinical remission of tuberculous meningitis is seen in the vast majority of treated cases irrespective of the gravity of the clinical picture with initial treatment; few eventually survive. Relapses are common, almost expected by those treating the disease in any numbers. The failure to observe prolonged or even permanent remission of the disease has often been explained by the emergence to predominance of tubercle bacilli wholly resistant to the antibacterial effect of streptomycin. Although, on the surface, clinical relapse seems closely associated with a change in bacillary susceptibility—it occurs at a period when resistant organisms are expected in other forms of tuberculosis treated with streptomycin—actually it is quite unusual to find streptomycin-resistant tubercle bacilli in the central nervous system even after prolonged exposure to streptomycin. Study of, and explanation for, this basic discrepancy rests with bacteriologists. The clinician, on the other hand, must at all times be consciously aware of three possible ways to circumvent the almost inevitable relapse: (1) early and adequate treatment in the hope of eradicating the infection prior to permanent and irreversible brain damage; (2) addition of paraamino salicylic acid, and/or possibly a sulfone, to delay resistance and to offer increased antibacterial protection; and (3) prolonging or reinstituting treatment promptly in the face of obvious clinical relapse in the hope that some microorganisms at least remain susceptible and continued treatment useful."

Hormone Deficiency During Menopause and Old Age. The Receptivity of the Organs to the Action of the Estrogens — WEBER, ERIC — *Gynaecologia*, 129: 37 (January) 1950.

Aging of the ovaries and the involution of the genital tract which depends on it do not always go parallel. Thus at the beginning of the menopause the follicular apparatus sometimes persists for a long time in activity instead of undergoing progressive atrophy, and the endometrium is maintained in a phase of proliferation, manifested by menorrhagias or metrorrhagias. This condition used to be termed metropathy and corresponds to Zondek's hyperfolliculinic condition or Watson's common hyperfunctional condition. Watson in addition distinguishes a secretory hyperfunctional condition with persistence of the activity of the corpus luteum and provoking the same symptoms. However, apart from these special and uncommon cases the symptoms of the menopause and of old age are symptoms of estrogen deficiency. While in transitory hormonal deficiency in the young woman the manifestations are limited almost exclusively to amenorrhea and endogenous vaginitis the disturbances associated with definite aging of the ovaries are much more diversified. The systemic disturbances are of a metabolic, circulatory and neuropsychic nature and variable in degree; they are not caused exclusively by the hormonal disequilibrium and disturbances of the autonomous nervous system play a considerable part. Emotional irritability may make evaluation of the purely endocrine factor difficult, and it is certain that the menopausal disturbances are not always directly linked to a diminution of the blood estrogen level. Local modifications of the genital organs can be measured more accurately with respect to

extent and degree than the systemic and chiefly functional disturbances; this applies particularly to morphologic alterations in the genesis of which emotions play no part. In the presence of such phenomena the question may be raised whether effects of pure deficiency are dealt with or whether other etiologic factors play a part. The involutive processes are chiefly characterized by atrophy of glands, epithelium and muscles, and particularly the latter are replaced by connective tissue. There also may be sclerosis, keratosis, and various types of inflammation. Leukoplakia and vaginitis show best the modifications of the basic process by secondary complications which finally take first place. One writer demonstrated that some cases of vaginitis are not of bacterial but of hypo-ovarian origin; ovarian hypofunction leads to atrophy of the vaginal epithelium with disappearance of the glycogen and a rise of the *p*H, and only secondarily to development of a pathogenic flora.

In some cases involution of the genital organs is not associated with any pathologic symptoms. The regressive process usually extends uniformly over the entire genital tract, but different tissues and segments may participate unequally in atrophy and shrinkage. Halban's annular subhymenal cirrhosis represents a special limited form of involution, characterized by formation of a ring of rigid connective tissue at the base of the hymen, comparable to a thin tense cord, with difficulties on cohabitation. Another type of typically localized involution is represented by Labhardt's kraurosis of the vaginal fornix; according to Wenner this condition includes marked proliferation of the perivaginal connective tissue and more or less intense destruction of the epithelium above the stenosis, while below the vagina preserves normal caliber and elasticity and intact epithelium. Fornical kraurosis is relatively frequent after intrauterine curietherapy but also occurs without it. Labhardt also described another type; namely, involutive stenosis of the external orifice with hematometra, in the form of spontaneous shrinkage without preceding inflammation, as opposed to the stenosis subsequent to treatment with caustics. Under the term of atrophic parametritis an alteration of the pelvic connective tissue has been described, characterized by retraction of the ligaments, particularly the sacrouterine ones, on the basis of menopausal involution rather than an inflammatory process.

Some young women show delayed development or deficiency disturbances of a well delimited portion of the genital tract, like uterus or vagina, and in the hypohormonal conditions of the menopause and old age involutive processes may also be limited to tissues of a certain area; compared to other portions of the genital tract such areas will frequently prove rather refractory to hormonal treatment, even in adequate dosage. These two groups of pathologic conditions represent a local reduction of receptivity to the hormone effect, both with respect to origin and response to treatment. The problem of receptivity and nonreceptivity is thus not a purely endocrinologic problem and its solution is not merely a quantitative one. The uterine blood supply depends on the neurovegetative system, but particularly in senile involution anatomic factors rather than vasomotor phenomena seem to be dealt with. Thus one writer explains the typical localization of the trophic disturbances in kraurosis of the fornix by arteriosclerotic processes which affect with preference this region where the last ramifications of the two arterial networks are encountered. Old inflammatory processes have been invoked in other cases as cause for nonreceptivity but such processes are frequently unilateral while the trophic disturbances are always definitely symmetric.

Hormonal treatment of the menopause is not limited to the ovarian hormones; if the main symptom is a menometrorrhagia the estrogens often cannot be used, and if curietherapy or hysterectomy are not indicated male sex hormones may give interesting results; their hemostatic effect has been known for a long time while their effect on the systemic disturbances is still little known. One explains it by inhibition of the pituitary hyperfunction which follows the menopause. In favorable cases 10 to 25 mg. of testosterone will control hemorrhage and the systemic symptoms, while the local disturbances may require much higher doses. Wenner and Joël controlled headaches and stubborn vulvar pruritus with a dose of up to 375 mg. within two weeks, but with doses above

300 mg. per month masculinization has to be feared. Male sex hormones have been recommended in cases with a history of cancer or even endometriosis as heterologous sex hormones impede development of malignant tumors while the homologous ones stimulate it.

Except in the hypersecretory state and the special cases outlined hormonal treatment of the menopause is based on the ovarian hormones, and particularly the estrogens. Experience shows that in old women the combination of estrogens and progesterone does not improve the results of estrogens alone. It is well known that the results of isolated hormonal treatment of the menopause are often fallacious in the presence of marked disequilibrium of the autonomic nervous system, and in such cases sedatives should also be used; some authors give only sedatives in such cases and reserve the hormones for severe deficiency states but the author considers maintenance of the cycle a legitimate goal even in the absence of serious symptoms. Furthermore, prophylactic hormonal treatment seems the only means of preventing anatomic fixation of the hormonal deficiency in predisposed areas. Therefore, the author recommends systematic hormonal treatment of the menopause as the estrogens act not only on the sex but also on the metabolism. Under these circumstances relatively small doses may be sufficient (1 mg. per week). The rhythm of treatment should be adapted to that of the ovaries in order to imitate the endocrine physiology. In old age, however, cyclic treatment is no longer required. Choice of preparation, form and rhythm of administration, and dosage depend on experience and clinical response; the results may be controlled by examination of vaginal smears which will show disappearance of the leukocytes and appearance of keratinized polygonal cells. In the beginning the injectable preparations are preferable but once the syndrome is under control peroral or perlingual treatment may be resorted to. Particularly the synthetic preparations are not always well tolerated by the digestive tract. In predominantly local disturbances local estrogen treatment gives interesting results. Implantation of estrogen crystals or pellets is disputable in young women but is advisable in old women when the uterus is absent or has been functionless for a long time as after curietherapy, and under these circumstances menacing hemorrhages will not occur; recently implantation into the perivaginal tissue has been advised.

Local postmenopausal lesions often require large doses, sometimes more than 10 mg. per week; in such cases the capacity of the estrogens to improve the peripheral circulation in general or the trophism of an organ is used rather than their specific sexual qualities. The peripheral vasodilatation, favored by the hormones, may be strengthened by certain sympathicolytic drugs like yohimbine and priscol, and by parasympathomimetic drugs like acetylcholine prostigmine and pilocarpine. In confirmation of another's work the author demonstrated that by the intermediary of the parasympathetic system pelvic hyperemia can be provoked, manifesting itself in the young woman often in the form of a "menstruation." The effect is not as evident in old women, but observation shows that certain tissues, having become rigid due to prolonged hormone deficiency and being refractory to isolated hormone treatment, will sometimes change their consistency when hormone treatment is combined with 0.5 mg. of prostigmine daily for a week. Prostigmine is also an excellent drug to combat the gastrointestinal intolerance to the estrogens.

Diabetes. Certain Basic Considerations — Ohler, W. Richard — *New England Journal of Medicine*, 242: 245 (February 16) 1950.

Because of present interest in the detection of the patient with unrecognized diabetes the writer presents a few basic considerations in relation to this disease.

"Diagnosis.—A single positive urine test does not mean diabetes, nor does a single negative test exclude it. An accurate diagnosis cannot be made without both urine and blood studies, and even then there are many cases in which the diagnosis may remain in doubt. Given the typical diabetic symptoms of weight loss, polydipsia and polyphagia, together with glycosuria, 9 times out of 10 the diagnosis of diabetes is correct without a blood sugar determination. However, many diabetic patients

have no symptoms and exhibit glycosuria only occasionally. Briefly, there are a few rules that will aid in a positive diagnosis.

"Glycosuria in addition to a fasting blood sugar of 130 mg. per 100 cc. or over means diabetes. Glycosuria and a normal fasting blood sugar may or may not mean diabetes. In such cases some sort of tolerance test must be done. Examination of the urine and blood for sugar 45 to 60 minutes after a meal liberal in carbohydrates is helpful. Glycosuria in combination with a blood sugar of 180 mg. per 100 cc. or over probably means diabetes. At any rate, the subject can be called a strong diabetic suspect.

"Glucose Tolerance Test: Generally speaking, the most common procedure is to give 100 Gm. of glucose after a fast of at least 12 hours and after a period of three days during which there has been no restriction of ordinary diet. Urine and blood tests are made before the glucose is ingested and at various intervals thereafter, usually periods of one, two and three hours. In the normal person one expects that the blood sugar will not rise above 180 mg. per 100 cc. and that the level will return to normal two or three hours after the glucose meal is given. Most observers agree that a peak value, even though accompanied by glycosuria, is not diagnostic of diabetes if the blood sugar returns to normal in two hours.

"Differential Diagnoses and Diagnostic Pitfalls.—Renal Glycosuria: In this condition glycosuria occurs without hyperglycemia. Sugar may appear in the urine at all times or may depend upon the type of diet, but at no time is there elevation of the blood sugar. This condition is not harmful and apparently never develops into true diabetes.

"Sugars Other Than Dextrose: Occasionally, but not frequently enough to be of practical importance, reducing substances other than dextrose are present in the urine.

"In pregnancy, lactose may be present. In addition, the renal threshold in pregnancy is low. It is possible, therefore, that the sugar found is more likely to be dextrose than lactose. A blood sugar determination will satisfy diagnostic requirements and will eliminate a false sense of security, which on occasions has led to real trouble.

"In addition to points already made, the underlying difficulty in all diagnostic tests for mild diabetes is due first to the fact that the rate of absorption of glucose and also the renal threshold for sugar may change from time to time, and secondly to the fact that there are a number of diseases that may influence the blood sugar level, such as infections, recent injuries, acute alcoholism, hyperthyroidism, hypertension, certain adrenal tumors, encephalopathies, coronary occlusion, renal failure and arteriosclerotic changes in the kidney.

"Accordingly, it is difficult to see how one has any right to make a positive diagnosis of diabetes without certain laboratory tests as heretofore enumerated, as well as a carefully taken history and physical examination of the patient."

Detection Drives.—"The nature of diabetes is such that if untreated the mild case frequently changes to the severe type. As a matter of fact, the physician has his best opportunity to do a real, constructive job in the intelligent management and careful follow-up study of the patient with mild diabetes. In no case should the finding of even a trace of sugar in the urine be disregarded."

"Regardless of all that can be said about the importance of finding the hitherto unknown case, certain other aspects of diabetes detection are worthy of careful consideration.

"The first is the very important problem of erroneous diagnosis. . . . The main consideration is that there is a possibility of an erroneous positive diagnosis. Moreover, there are many cases in which patients must be observed for a period before a previously questionable diagnosis can be ruled in or out."

"Detection drives if instituted at all should include wholehearted support of physicians involved, a period of instruction for physicians regarding methods and interpretation of diagnostic procedures, and careful marshaling of various forces such as hospital clinics, health agencies, visiting nurses and social agencies to assure adequate laboratory facilities, a careful follow-up study of suspects, and, finally, a plan definitely agreed upon for reporting to some central agency or physicians' com-

mittee regarding the results of follow-up study. There is no point in merely referring a patient with a positive urine test to the family physician until one is certain that the physician will accept the responsibility involved and that proper laboratory facilities are at his disposal. Any hit or miss method in the diagnosis of any disease is just as likely in the long run to do harm as to do good."

Management.—The object is to keep all patients at work without interruption because of episodes of hypoglycemia or severe acidosis, and without serious late vascular complications as evidenced by retinal changes, heart and kidney damage and peripheral vascular disease.

The whole subject of diabetic control may be briefly summarized as follows: In the newly discovered case it is probably desirable to treat the patient vigorously—in other words, to try to keep both urine and blood sugar normal in the hope that rapid actual pancreatic regeneration may result.

"Once it has been determined that there is no hope for rapid pancreatic regeneration, or once it is clear that the patient needs 30 units of insulin or more, vigorous so-called purist treatment may not be necessary or practicable. . . . A conservative attitude may be advisable. The problem here is to keep the diabetes in as good control as possible without interruption by insulin reaction or acidosis." In the writer's clinic, the treatment of diabetic patients is almost always of the conservative type—with an effort to keep patients at work and with particular care to avoid insulin reactions. "This means that most of the patients have some glycosuria at times during the day and that the fasting blood sugar levels are seldom within normal limits. Also, little or no attention is paid to high blood sugar levels without glycosuria, in the belief that hyperglycemia without glycosuria is not harmful. Nevertheless, in an appreciable number of these patients it has been possible over the years to reduce the amount of insulin and in not a few, insulin has been discontinued."

The writer's clinic has had no experience with the so-called "free dieting" type of treatment.

"Diet: In general, the diabetic diet does not differ greatly from the average diet. Most patients receive at least 150 Gm. of carbohydrates, and many receive as high as 300 Gm. The fat is definitely reduced—80 to 150 Gm.—and the protein should be rather high—100 to 150 Gm." It seems to the writer that a rather high level of carbohydrate (200 Gm. or more) and of protein (100 to 150 Gm.), with a fat diet less than 150 Gm., is about right.

Weighed Diets: In the writer's clinic it has not been possible to use weighed diets, for which he can see no necessity. "Printed diets, using household equivalents, are sufficiently accurate for all practicable purposes. Certainly, in the type of working person under consideration, this type of diet has worked satisfactorily. However, one good way to learn about diet values is to be forced to weigh the diet."

"Complications.—Obviously, the best way to treat diabetic complications is to prevent them and the second best way is to discover them early."

Education of the patient is of great value. Education of the general practitioner to include simplification of methods, and improvement in laboratory facilities, is equally important but has been neglected.

"The physician who assumes the responsibility for treating a diabetic patient needs to know a few simple rules. There is no mystery about dietetic management—weighed diets are not necessary; all the physician needs is a very simple printed program, easily understood by both himself and the patient. Insulin is a potent drug; its institution should be started slowly, and changes made gradually. The presence of acidosis is a definite danger signal, requiring vigorous treatment for at least a brief period. In every case careful attention should be directed to the state of the peripheral circulation, and to the patient's general physical condition."

"How often should the diabetic patient be seen by his physician? Obviously, this depends entirely upon circumstances. Some patients need to be seen once a year, and others may need attention every day or several times a day. The main point is that the responsibility rests entirely upon the physician himself."

Acidosis and Coma: "X-ray examination of the chest, blood cultures and com-

plete urinalysis should be the rule in any case of severe acidosis. It is well to remember that in the badly dehydrated patient frank pneumonia may be present without any demonstrable physical signs.

"Secondly, so far as statistical data are concerned, and also so far as the proper point of view of both the public and the general practitioner is concerned, it would be a great help if those interested in diabetes could unite on what is meant by the term 'diabetic coma.' In some clinics all patients with blood carbon dioxide values of 20 volume per cent or lower are considered to be in 'coma,' and in other clinics the term 'coma' is used to designate only the unconscious patient."

Diabetic patients in coma present a real problem, and deaths do occur. "On the other hand, regardless of the degree of acidosis, the management of the conscious patient presents no serious problem despite the fact that in this group blood carbon dioxide values may be as low as 8 volume per cent."

Vascular Disease: "The diabetic person is an ideal patient for the study of possible early vascular disease and therefore commands the attention of all physicians interested in this problem."

"There are many patients who have survived 25 years of the disease and who are to all intents and purposes perfectly well. Many more have had the disease for 25 years or more and are not perfectly well but are able to carry on with comfort. In addition, there is always the possibility that unexplained changes will take place."

The Use of a Cholinergic Agent in Diagnosing Borderline Cardiac Disease — BUFF, I. E. — *West Virginia Medical Journal*, 46: 1 (January) 1950.

"Tachycardias of certain origins can be easily differentiated and diagnosed by means of electrocardiography. For example, anyone with basic knowledge in this field can distinguish easily a case of paroxysmal auricular tachycardia from one of paroxysmal ventricular tachycardia. Physiologic tachycardia, such as that frequently observed when an electrocardiogram is being taken for the first time, is also rather simple to diagnose. However, in the latter instance, certain 'abnormalities' may be seen in the tracing which, to the inexperienced clinician, are at times misconstrued as evidence of myocardial damage. For example, the P waves may vary somewhat from the normal standard, or there may be a slight depression of the S-T segment. While it is true that such minor deviations from the normal may indicate cardiac damage, it is not true in every case, especially when tachycardia is present."

In the writer's practice it has been customary for several years to use prostigmine in aborting attacks of supraventricular tachycardia. "It is believed that prostigmine decreases an abnormally high cardiac rate through the medium of vagal stimulation.

"It was decided to use prostigmine empirically in cases of simple sinus tachycardia with minor electrocardiographic changes to determine whether the drug would reduce the heart rate to normal and thereby possibly alter the electrocardiogram. This has been done in a series of approximately 60 cases. In each case the subcutaneous administration of 1.0 mg. prostigmine methylsulfate not only reduced the heart rate, but apparently was responsible for the disappearance of the electrocardiographic abnormalities noted on the pretreatment tracings.

"The following 3 case histories are representative:

"Case 1.—C. P., male, aged 38 years. The patient complained of vague precordial pain unrelated to exertion. Physical examination of the heart revealed no abnormalities. An electrocardiogram showed a cardiac rate of 94 per minute in standard leads and 112 in AV leads. The P-R interval was 0.16 second; P waves were enlarged; the S-T segment was depressed 1.0 mm. in leads II, III and aVf, and 0.5 mm. in leads V_5 and V_6. This could be interpreted as being indicative of myocardial damage, auricular hypertrophy and possibly early left ventricular hypertrophy (V_5 and V_6).

"Because of the suspicion that these changes were physiologic and due to the moderate degree of tachycardia, a subcutaneous dose of 1.0 mg. prostigmine methylsulfate was given. Twenty minutes later another tracing was obtained. This revealed a cardiac rate of 75 per minute

and no abnormalities whatsoever. A diagnosis of intercostal neuritis was made.

"Case 2.—H. I. A., male, aged 24 years. The patient gave a history of having been diagnosed two years before as having rheumatic heart disease. His activity was sharply curtailed and a rather severe cardiac neurosis developed.

"Physical examination revealed no gross abnormalities. An electrocardiographic tracing demonstrated a cardiac rate of 100 per minute, the P-R interval was 0.21 second, and there were enlarged P waves in leads II, III and aVf. These changes could well be interpreted as being indicative of auricular hypertrophy with rheumatic heart disease.

"The patient was given 0.5 mg. prostigmine methylsulfate subcutaneously and another tracing obtained 20 minutes later. This revealed no changes in the P waves and a P-R interval of only 0.20 second, the upper limit of normal.

"Case 3.—V. S., female, aged 74 years. The patient was seen for a routine physical check-up. There were no subjective symptoms. Physical examination revealed retinal changes, interpreted as being due to arteriosclerosis. Blood pressure was 180/94 mm. Hg, but the heart sounds were normal with no murmurs.

"An electrocardiogram revealed a heart rate of 100 per minute and a definite S-T depression in leads V_4 and V_5, especially in the latter. This could justifiably be interpreted as being indicative of left ventricular hypertrophy (secondary to the hypertension). After a subcutaneous dose of 1.0 mg. prostigmine methylsulfate a second tracing revealed a cardiac rate of 83 per minute. The S-T depression in leads V_4 and V_5 had completely disappeared. The patient was diagnosed as having an essentially normal heart."

"The 3 typical case histories are revealing in that they demonstrate that certain individuals with cardiac-like symptoms and a suspiciously abnormal electrocardiogram in the presence of tachycardia can be easily incorrectly diagnosed as having disease of the cardiovascular system. While this mistake may not be too serious in some cases, it may be a tragedy in others. It is especially deplorable when one is dealing with a child or young adult, in either of which case the psychic consequences might be sufficiently grave as to lead to serious personality change.

"An urgent plea is made that all such individuals be examined with great care and a second electrocardiographic tracing obtained following the administration of 1.0 mg. prostigmine methylsulfate if the first tracing reveals tachycardia. It is believed that this means a substantial number of patients who otherwise might be converted into cardiac cripples can be reassured that they possess an essentially normal cardiovascular system."

Is Field Nephritis a Mercury Fulminate Poisoning? — Ledergerber, E. — *Schweizerische medizinische Wochenschrift*, 80: 51 (January 21) 1950.

The author observed in mercury fulminate poisoning renal affections resembling field nephritis and therefore discusses these two conditions comparatively. Both affections are the results of war and war industry, but in the field other affections cover, complicate or confuse the picture of field nephritis and the latter assumes a special character depending on circumstances; it is often confused with edema but the edema of field nephritis, like that of glomerulonephritis, contains more than 1 per cent of protein while in uncomplicated edema the protein concentration is approximately 0.1 per cent. However, when field nephritis is prolonged and leads to hypoproteinemia and cholesterolemia the edema becomes poorer in protein.

Descriptions of field nephritis mention as prodromal signs upper respiratory catarrh, cough, dyspnea, subfebrile temperatures, cervical glandular swellings, headache and backache; the prodromal stage may be acute or insignificant, and may last several days or be lacking. There is no definite interval between prodromes and field nephritis as observed in scarlet fever or tonsillitis. Diarrhea may occur and the liver and spleen are often enlarged. Cardiac insufficiency appears early and causes stasis, dyspnea, pulmonary edema, hepatomegaly, cardiac asthma, cyanosis, fatigue and other signs. In addition to the cardiac stasis another cause for the edema is assumed and the edema is always intense and appears early. The extrarenal disturbance of the water metabolism is

associated with inhibition of the sodium chloride excretion. Transitory hypertension is usually encountered during the acute stage. Bradycardia and widening of the QRS complex with lengthening of the T wave may occur. At first there is polyuria, particularly at night, while later oliguria with a highly concentrated urine supervenes, up to a specific gravity of 1.040. Anuria is rare and only rarely fatal. The urine contains abundant albumin, leukocytes and casts and the hematuria ranges between traces and massive bleeding. Improvement often supervened within a few days, but mild albuminuria and hematuria often persisted. Abortive forms may be observed in addition to the fully developed ones, and physical strain or infections may transform the former into the latter, or provoke a recurrence of the latter. The anatomic findings are those of congestion of the kidneys; in the early stage only immense blood filling of the glomeruli may be found, while advanced stages sometimes show reduction of the arterial blood supply. In rare cases characteristics of chronic nephritis supervene. The sedimentation rate is high and subject to marked variations; the blood is thickened. The vegetative nervous system shows definite lability. Rheumatic pains are often complained of, and also paresthesias. Alterations of the arterioles were found on muscle biopsies.

An infectious origin of field nephritis has been assumed but transmission has never been achieved. Focal infection as cause was rejected on the basis of 67 useless tonsillectomies. In a factory where mercury fulminate is produced the author observed poisoning with this substance and the syndrome resembled closely that of field nephritis. Catarrhal phenomena with regional enlargement of the lymph glands are frequent in both conditions; as the mercury in the form of vapor or dust directly affects the upper respiratory tract it damages the mucosa by direct contact and is partly absorbed and detained in the regional lymph glands causing their enlargement. The tendency to local infections is thus accounted for. Systemic mercury poisoning would then lessen the defense against infections generally, and combat soldiers show an extremely high susceptibility to infections. One writer described systemic reduction of defense in severe and often fatal mercury oxycyanide poisoning; superimposed infection aggravates then the mercurial nephrosis. Anatomically an inflammatory-infectious component caused by streptococci is found. The frequent finding of streptococci in the tonsils is considered as an associated sign rather than the main causal factor of field nephritis. Penicillin will be effective only against this secondary infection.

After explosion mercury fulminate evaporates rapidly in the open, but in stationary warfare and in protected positions the mercury vapor persists longer in the air and is precipitated at the walls and clothing, so that the soldiers inhale a considerable amount after some time. Therefore the mercury poisoning, latent at first, may become acute at any moment, and possible provoking factors include strain, injuries, infections and exposure to cold. As the infantry uses mercury fulminate more than any other branch of the service it is understandable that 90 per cent of all cases of field nephritis occur among these troops.

According to one writer about one fourth of the mercury vapor which reaches the lung with the air of inspiration is absorbed; the mercury is taken up by blood and lymph and urinary and fecal excretions start immediately. If the intake is moderate excretion may keep up with it and little mercury will be deposited in the tissues, but if the intake exceeds the excretory capacity the mercury blood level will rise and storage in the tissues will increase. The first systemic damage is represented by the disturbance of the water metabolism; the diuretic effect dehydrates blood and tissues and the increased diuresis leads to increased mercury excretion, but if not enough water is available diuresis and mercury excretion will diminish. The insufficient water contents may be aggravated by deficient water intake, increased perspiration, vomiting and profuse diarrhea, resulting in increased blood viscosity as described in field nephritis. The acute stage of the latter represents a renal congestion for which three components may be made responsible; namely, cardiac insufficiency with lacking vis a tergo, the direct congestive effect of mercury on the kidneys, and the vasodilator effect of the nitrites of mercury fulminate. Depending on the intensity of these three factors all stages

between slight slowing down of the blood stream and complete circulatory arrest with blockage and thrombosis of the glomerular loops may be produced. The slowed circulation causes tissue damage by anoxemia and a prolonged stay of the toxins, that is the mercury in the case under consideration, with resulting glomerular damage. A slowdown of the intensity of renal stasis will lead to microhematuria by diapedesis, slight albuminuria, oliguria, and a urine of high specific gravity while intense and prolonged stasis will lead to marked vascular damage with massive hematuria and albuminuria. During oliguria blood and tissue will retain increasing amounts of substances normally excreted by the kidneys, and these substances will draw water into the tissues, leading to edema of the loose connective tissue of all organs. The kidneys will become enlarged and tense, the initial congestive hyperemia of the cortex will subside because of reduction of the blood supply by the pressure of the edema on the thin-walled cortical vessels, and anemia will result and persist until the edema subsides. Persistent edema will damage the nephrons considerably, and cellular infiltration of the interstitial tissue will supervene. The scanty and abnormal glomerular filtrate will be reabsorbed almost completely by the tubules with resulting poisoning and functional impairment, and desquamation and cast formation will obstruct part of the tubules.

The latent mercury poisoning of stationary warfare represents a strain on the circulation of the kidneys and any additional strain may almost suddenly provoke field nephritis. Exposure to cold cannot be considered the cause of field nephritis as it is never found in participants of winter expeditions and in hunters, and a connection with tonsillar infections has never been demonstrated convincingly. Cold weather may play a part in that the soldiers then will spend as much time as possible in warm mercury-poisoned rooms, that the air becomes drier and causes greater water loss by respiration, and that water is also lost by increased diuresis. Many diseases and poisonings with water-lack and toxicosis cause a tendency to renal affections. Soldiers may even bring enough mercury home on their clothing to produce field nephritis in others. This also explains the involvement of hospital attendants behind the front. Another objection concerns the differences between mercury fulminate poisoning and field nephritis. Thus cardiac disturbances and edema are more marked in the latter, but this difference is partly due to the fact that the munitions contain poisons other than mercury fulminate as well, changing the character of the affection, and that the soldiers live under conditions different from those of munition workers: The clinical and anatomic findings of field nephritis and mercury fulminate poisoning are similar, and the same findings, only in a more severe form, are encountered in sublimate poisoning.

It was demonstrated that Feer's disease results from calomel administration in the usual dosage; this disease frequently shows a severe renal involvement with albuminuria, casts and massive hematuria, and hematotoxic conditions with eosinophilia, leukopenia or even agranulocytosis, hepatomegaly, splenomegaly and extensive edema; neurotoxic and vegetative symptoms and the hypertension of the acute phase were also found, like in field nephritis and mercury fulminate poisoning. Children affected by calomel often showed glycosuria without hyperglycemia, and in workers of mercury fulminate no diabetes was found over a period of 30 years, while they frequently showed low blood sugar values on glucose tolerance tests. Perhaps the mercury has a direct reducing effect on the sugar or enzymatic processes are dealt with.

Healing with defect was reported in about half the cases of field nephritis, but the residual symptoms are usually mild and stable and deaths are rare. After World War II much lower figures for healing with defect were reported, and similar figures apply to the mercury fulminate workers observed by the author. Contrary to all other types of hematogenous nephritis, field nephritis does not lead to chronically increasing vascular damage in the course of years after the attack, indicating that field nephritis is not a true kidney disease but a complex of symptoms within the framework of mercury fulminate

poisoning, and associated with severe metabolic disturbances. As long as the latter is not controlled disturbances will persist, particularly involving the vegetative nervous system and the gastrointestinal tract.

Serum Albumin in the Treatment of Toxemias of Pregnancy — DORR, EDWARD M. — *Nebraska State Medical Journal,* 35: 32 (February) 1950.

It is the writer's purpose to give his experience with adjunct therapy in the treatment of a group of toxemia patients.

The treatment of the group the writer discusses varies little as to whether the patient has a nephritic toxemia or a severe preeclamptic toxemia. "Unless a definite history of nephritis is obtained before these patients develop symptoms, kidney function tests, eyeground findings, etc., may be confusing." It has been the writer's experience that the correct diagnosis, in many women, cannot be made for at least three to six months after delivery.

"These women constitute a group which are forerunners of eclampsia and if not seen early and treated adequately will develop convulsions." This group the writer has reference to, presents the following findings: "a history of headache of varying degrees, lassitude, generalized swelling of the extremities and face, some with spots before their eyes and some with epigastric distress. Physical examination reveals blood pressure increase, in many instances very high, generalized edema, albuminuria, and eyeground findings.

"These patients must be hospitalized for treatment and kept under close observation until the pregnancy is terminated. The above clinical picture usually develops during the last trimester and occurs more frequently in women with their first pregnancy."

"Urinary and blood proteins have been studied by various workers. There is excreted a large amount of serum globulin and serum albumin in preeclamptic and eclamptic patients. The amount excreted is considerably more than in cases of nephritis or nephrosis. The serum albumin molecule is smaller than the serum globulin molecule, hence passes through the injured glomerulus more readily." The writer feels that the heavy protein deficiency in the blood plasma is conducive to edema. "In most instances the decrease in the amount of edema is accompanied by an improvement in blood pressure readings and the general condition of the patient." One must always keep in mind the patient who has very little fluid retention in the tissues and still has severe preeclamptic symptoms.

"The use of various substances, particularly colloidal in nature, to increase osmosis and to relieve edema, has been described for various conditions. The principal physiological condition is to obtain dilution of the blood." The writer has found that concentrated glucose does not always fulfil this desired effect, hence he has used 10 per cent or possibly 20 per cent glucose. "Good functioning kidneys, relieving anuria and reducing edema, are of prime importance. With the relief of edema, the reduced edema of the brain prevents convulsions. Those patients who have died of eclampsia demonstrate the significant brain involvement."

"The addition of serum albumin should increase blood volume, decrease viscosity. If this condition can be attained, the filtrable ability of the glomeruli will be enhanced.

"With the above explanation in mind it was thought that serum albumin might be given with good results. Blood plasma has been used in the treatment apparently with satisfactory results." Because of the lowered serum albumin of the blood and in many instances the loss of large amounts of serum albumin in the urine, the writer believed serum albumin would be more valuable. This has been somewhat true.

"Twenty-five patients, corresponding to the classification of nephritic or severe preeclamptic toxemias, were observed. . . . All of these patients were under close observation which can be done only in a hospital." The care of these patients at home, in the writer's opinion, constitutes poor medical care.

"Seven of the 25 women were classified as renal or nephritic toxemias. This diagnosis was made first, from a history of nephritis; second, from findings after admittance. A careful check-up a few months after delivery revealed that 4 of the remaining 18 also were nephritics." To the writer this emphasized one point in this

series that has been stressed many times before; chronic nephritis and pregnancy are incompatible.

"The nephritic patient should be advised against subsequent pregnancies and if she becomes pregnant, the pregnancy probably should be interrupted and the patient preferably sterilized. The life expectancy of such a patient, who carries an increased blood pressure and albumin after delivery, is shortened markedly; each succeeding pregnancy shortens it more.

"Four patients had little or no edema but increased blood pressures and albumin. None of these responded well to treatment, necessitating emptying the uterus after 12 to 24 hours' observation. The toxemia patient without demonstrable edema is difficult to treat and usually must be interrupted after a relatively short observation period.

"All patients were put on a routine management, bed rest, sedation, either morphine or barbiturates, salt free, high protein diet. Fluid intake and output were recorded. Retention catheters were used frequently, especially in those patients with a low output. A low urinary output or an anuria before or after delivery is serious; the outcome is bleak indeed unless kidney function is restored.

"Fluid intake was limited to 2,000 cc. the first 24 hours and increased to a maximum of about 2,500 cc. thereafter. Considerable debate still exists as to the amount of fluid such a patient should have. Ten per cent glucose intravenously was used routinely. One hundred twenty-five cubic centimeters of serum albumin or 25 Gm. of albumin, was given every 6 hours for the first 24 hours; if the response was not adequate this was continued. If the clinical symptoms improved, the amount of serum albumin was reduced. Thirteen of the 25 patients showed marked improvement the first 24 to 36 hours, 5 were improved. The last 7 patients all were delivered within 24 to 48 hours, although improved but not sufficiently to continue conservative treatment. Of the 13 markedly improved, 7 were delivered before 72 hours because of signs of increased blood pressure, edema, etc. Six had spontaneous labors either with medical induction or rupture of membranes or normal onset of labor. Seven of the 25 patients did not improve with treatment and were delivered either by induction of labor or cesarean section. None of the above patients had convulsions."

The writer has adopted rather a strict rule in regard to the time of delivery of all severe preeclamptic patients except those with eclampsia. "If a patient does not improve with treatment within 12 to 36 hours or if after improvement there is a return of symptoms or clinical findings, delivery is consummated. The procedure used depends upon the number of weeks gestation, condition of the cervix, the station of the head, multipara or nullipara. If conditions for delivery from below are not suitable cesarean section is advised." The writer feels that conservative treatment is carried on too long in many instances, with the result of poorer risk to deal with in the end.

Investigation of the Smog Incident in Donora, Pennsylvania and Vicinity — Townsend, James G. — *American Journal of Public Health*, 40: 183 (February) 1950.

The writer discusses the year-long investigation by the Division of Industrial Hygiene of the Public Health Service into the smog episode that occurred last fall in the town of Donora, Pennsylvania.

"Donora is a steel mill town of some 13,000 residents, sitting on a hillside on an inside curve of the Monongahela River 30 miles southeast of Pittsburgh. Donora and the small community of Webster on the other side of the river are both backed by hills that rise some 400 feet above the river level. The curve of the river and the hills form a natural bowl which can—and did in this instance—lead to the bottling up of air on the valley floor for lengthy spells. The three plants of the big steel mill manufacture steel, wire, and zinc, products, and almost all of the working population of both towns are employed at the mill, which operates on a 24 hour basis.

"River traffic, largely coal from the coal fields to the mills in Pittsburgh, at this point on the Monongahela ranks in terms of tonnage with the highest in the world. From the considerable number of railroad trains, both through trains and local ones inside the yards, and the homes, and stores

of the town which also burn coal, there is contributed a sizable amount of smoke and air pollution in the little valley, on top of the tremendous load emerging from all of the stacks of the three plants on the river bank."

"Smogs" are nothing new to Donora. "They come often in the fall and spring, and usually last a day or so, until winds coming from one or the other end of the valley—or across the hills on either side—blow them away. . . . It was that familiarity with smog in Donora which prevented the people of the town from suspecting anything unusual when a smog blanketed the town on a Wednesday of the last week in October of 1948. It was the smog season. But this one stayed longer than usual and became worse than usual. And the longer the blanket kept the air bottled up, the heavier became the concentration of contaminants in that stable air. The first death occurred about 2 A.M. Saturday morning. By late Saturday night 17 deaths had occurred and hundreds were very sick. On Sunday afternoon the rain came, and shortly thereafter the smog went away."

The following week a team of 25 varied technicians moved into Donora to study every possible angle of the episode. "The team had two main objectives—to find out precisely what caused the deaths, and to establish ways and means of preventing future tragedies of this kind."

"The nurses—five of them—set out to visit one third of all the homes in the two towns, with the intention of getting a complete record of all illnesses or affections in each family during the smog."

"At the same time the physicians were interviewing a selected group of persons who had been definitely ill during the smog." These interviews were conducted in an office, and posed a number of problems.

"As a vital part of the medical investigation, a number of autopsies of the deceased persons had been planned." Yet because of prejudices and red tape it took several months of repeated visits to relatives, clergy, and cemetery officials before the physicians finally obtained all the permissions necessary to do autopsies on 3 of the fatal cases.

It was found that preexisting diseases of the cardiorespiratory system appeared as a single common factor among the fatally ill, and this finding was confirmed in the 3 autopsies performed. "The possibility of epidemic influenza was ruled out early in the study, and there was no evidence of excessive inhalation or ingestion of fluoride in the community."

The house to house survey revealed that 15.5 per cent of the total populace in the area were mildy affected; 16.8 per cent, moderately affected; and 10.4 per cent, severely affected. "It was also observed that both incidence and severity revealed a direct relationship with increasing age. Over 60 per cent of persons 65 years of age and over reported some affection from the smog, and almost one half of those were in the severely affected group.

"Of the many substances found in the atmosphere through engineering investigations, there were eliminated for consideration as causative agents those that were neither known nor suspected to be respiratory tract irritants. There were left for further evaluation as possible respiratory tract irritants fluoride, chloride, oxides of nitrogen, hydrogen sulfide, cadmium oxide, and sulfur dioxide, together with its oxidation products."

It was doubted that any one of these substances (irritant or nonirritant) by itself was capable of producing the symptoms observed. "However, a combination of two or more of these substances may well have contributed to those symptoms."

The well known fact that one substance may influence the physiologic action of another was considered and it is possible that there was a summation of the action of the individual irritant constituents which produced an effect greater than would be anticipated for any one of the individual constituents. "Moreover, there is evidence which indicates that the effect of irritant gases can be enhanced by adsorption on particulate matter. In addition to enhanced action, gases may be carried deeper into the respiratory tract than they would normally be carried in the absence of such particulate matter. This action would carry the noxious substance into the lower levels of the respiratory system where the more damaging effects would be produced.

"It is known that irritant gases exert their effect in the respiratory tract, depending largely on their solubilities; that is, compounds which are highly soluble exert

their effect in the upper respiratory tract while compounds which are less soluble exert their primary action in the deeper parts of the lung. A gas, therefore, such as sulfur dioxide which would normally exert its primary action in the upper part of the respiratory tract might produce more serious effects if it were transported to the deeper parts of the lungs, as, for example, by particulate matter. Both solid particulate matter and liquid particulate matter (fog) were present in the atmosphere in large quantities during the October, 1948, episode.

"Another influencing factor to be considered is carbon dioxide, which was probably a significant contributor to the overall atmospheric pollution load."

The engineering phase of the study has resulted in a number of specific recommendations and suggestions which should help prevent any recurrence of the tragedy in Donora. "Those recommendations should also prove valuable to other industrial cities and towns with geography similar to that in Donora."

It was recommended that the plants and other sources of pollution sharply reduce the gaseous contaminants—especially sulfur dioxide, which was found in considerable quantities—and particulate matter, which they emit into the atmosphere. "It was also recommended that a program of weather forecasts be established to alert the community to impending adverse conditions so that adequate measures may be taken to protect the populace.

"There is another reason why other cities should concern themselves with this new problem." In studying the weather history and mortality records of Donora, considerable evidence was found that Donora has gone through smog crises in the past without realizing what they were.

There was another major result of the Donora study, even more important in its long range aspects. "That was to raise the question of effects on health of living in a heavily contaminated area over a long period of time."

For years, during the long fight in this country to do away with the smoke nuisance, one has been without scientific data to assert that there was any threat to health in smoke. "But this is different." Here in these smog areas is not only smoke, but also contamination from gases and particulate matter, and it is believed that the Donora survey has shown beyond doubt that this combination can have an effect on health.

The starting point of the whole problem is more research. "The overwhelming public interest in the Donora study and other phases of the problem has put the Congressional wheels in motion, and bills and resolutions have been introduced urging action. Assuming the leadership at the federal level, the Public Health Service is planning to undertake a vigorous program of investigation. The time has come for the industrial hygienist in the state also to give serious consideration to this problem. Atmospheric pollution is no longer an optional field of activity—a fringe area of decided nuisance but of questionable health implications. The Donora study has erased any doubts that contaminants in the air can exact tolls on the health and lives of people."

Differential Diagnosis of Jaundice — Concílio, Generoso — *Boletim do Sanatório São Lucas*, 11: 83 (December) 1949.

An accurate early differential diagnosis of jaundice is of utmost practical importance. First, true jaundice must be distinguished from pseudojaundice; this will usually be possible on the basis of history and physical examination while rarely determination of the bilirubinemia may be required. While the yellow or greenish yellow coloration of skin and mucous membranes is caused by hyperbilirubinemia pseudojaundice spares the mucous membranes and is caused by drugs like atabrine or trypaflavine or by foods rich in carotene. True jaundice includes three main pathogenetic types; namely, the hemolytic, hepatocellular and obstructive ones, and once the type is determined the causal nosologic entity should be clarified, but treatment may have to be instituted before the etiology has been elucidated completely. A detailed history is of utmost importance and the same applies to a thorough physical examination.

Hemolytic jaundice results from a disturbance of the hemolytic-hematopoietic balance, with increased destruction of

erythrocytes leading to anemia and to an excess of bilirubin with resulting jaundice; the latter usually appears when the bilirubin level reaches three to four times its normal value. The diagnosis of this type is generally easy and this type amounts to only about 10 per cent of all cases of jaundice. Casual factors include a congenital factor of erythrocytic fragility, and toxinfectious or unknown hemolytic agents. A history of chronic jaundice with alterations of improvement and aggravation, and with other cases in the family, suggests hemolytic jaundice. The general condition may remain satisfactory for a long period of time. The jaundice is of the flavine type of Brusch's classification, is of little intensity, and generally not associated with pruritus and bradycardia; there is no preference with respect to age and sex. Splenomegaly is of great diagnostic value and splenic volume may be reduced up to 50 per cent with adrenalin. There is acholuria and hypercholia of the feces due to intense formation of urobilin bodies without fatty acids.

After exclusion of hemolytic jaundice the differentiation between hepatocellular and obstructive jaundice is of paramount significance, and it may be difficult as obstructive jaundice may cause secondary lesions of the liver cells and as patients usually come to examination at this stage. Hepatocellular jaundice occurs more frequently below the age of 40, while obstructive jaundice is more frequent above this age, mostly because of the greater incidence of neoplasm. Females are more often involved but cancer of the pancreas involves males in 90 per cent of the cases. A typical biliary colic precedes the jaundice in 84 per cent of the cases of calculous origin, and fecal elimination of calculi is of great diagnostic importance. Digestive and general disturbances before onset of the jaundice, including nausea, vomiting, anorexia, diarrhea and fever, usually attributed by the patient to alimentary indiscretions, speak in favor of hepatocellular jaundice although mechanical stone obstruction may be associated with biliary infection, fever, sweating and chills. Loss of weight, and an insidious painless progressive onset create a suspicion of neoplasm. Jaundice several months after surgical interventions at the level of the biliary tract may indicate lithiasis or stenosis of the choledochus or hepatitis from hemologous serum when transfusions were given. Hypocholia of the feces is present in both types, and complete acholia may be present in severe cases of hepatocellular and in total obstructive jaundice. According to one writer reddish yellow jaundice is characteristic of hepatocellular jaundice and greenish yellow jaundice of the obstructive type, with the black type as its culmination. Bradycardia was found in 70 per cent of the cases of hepatocellular jaundice and it was affirmed that parenchymatous liver processes determine hypotension due to portal hypertension which subtracts a certain amount of blood from the general circulation. Hepatomegaly is variable and diagnostically valuable only when highly marked, suggesting neoplasm or biliary cirrhosis. Splenomegaly is of great value; in mechanical jaundice the spleen is only exceptionally palpable, due to portal compression or hemolytic phenomena. Collateral circulation and ascites indicate a parenchymatous process, cirrhosis or cancer. Hemorrhages due to prothrombin deficiency may occur in either hepatocellular or protracted mechanical jaundice. The clinical course will contribute to diagnostic clarification. Neoplastic obstructive jaundice is progressive while calculous obstructive jaundice is frequently intermittent; hepatocellular jaundice usually lasts about four weeks. Jaundice of long standing, one to two years, with hepatomegaly and splenomegaly, suggests biliary cirrhosis.

The direct van den Bergh reaction is positive in both types of jaundice. Any serum giving the direct van den Bergh reaction also contains a variable quantity of indirect bilirubin; according to one writer the indirect bilirubin is always less than the direct one, but its share is larger in hepatocellular than in obstructive jaundice. Its normal concentration would be 0.3 to 0.5 mg. per cent, and it would be within or even below these limits in uncomplicated obstructive jaundice while it would rise to 1.5 mg. per cent in hepatocellular and in complicated obstructive jaundice. One has also shown that on treatment of certain icteric serums with ether the latter takes up bilirubin; this ether-extractable bilirubin is encountered

in total extrahepatic obstructive jaundice, that is in the majority of neoplasms. Another found that this occurs when the bilirubinemia exceeds 12 mg. per cent and that it is related to the phospholipid level, appearing when the latter exceeds 5 mg. per cent which occurs only in total obstruction of the choledochus. Thus ether-extractable bilirubinemia would be linked to complete obstruction of the bile ducts coinciding with good function of the hepatic parenchyma rather than to the presence of a tumor in itself, but would indicate cancer obstruction in 90 to 96 per cent of the cases. In total obstruction the feces will contain no urobilin bodies and a large amount of fatty acids, while in partial obstruction the latter will be diminished. In hepatocellular jaundice the urobilinogenuria is usually increased, except at the peak of the affection when it may be diminished for several days due to diminished bile flow into the intestine; repeated examinations are therefore indicated. In calculous jaundice the urobilinogenuria is usually normal, but in neoplastic obstructive jaundice it is markedly reduced or completely lacking due to lack of bile in the intestine. However, even in total obstruction the urine may contain urobilinogen as bilirubin impregnation of the intestinal wall permits passage of bilirubin and urobilinogen formation.

Contrast substances for gallbladder visualization derived from phenylpropionic acid are at present considered innocuous but in intense jaundice the gallbladder will not visualize regardless of etiology, and a flat plate will be of greater diagnostic help; still more important is roentgenologic examination of the duodenum which may reveal widening of the duodenal arc, compression or invasion in tumors of the head of the pancreas, and alterations of its descending portion in tumors of the ampulla or the terminal portion of the choledochus. A colorless duodenal fluid obtained by intubation, with lack of bile, and absence of urobilinogenuria will indicate total obstruction, but may occur at the peak of hepatocellular jaundice.

Absence of B bile indicates obstruction of the cystic duct. Subtotal obstruction will result in yellowish duodenal contents and discolorated feces, while partial obstruction will result in a yellow duodenal fluid and dark yellow coloration of the feces. Microscopic examination of the C bile may furnish interesting data; particularly in the initial phases of hepatocellular jaundice it will reveal an increased amount of mucus, more or less intensely bile-stained cellular elements, and bile cylinders, while the presence of blood will suggest a tumor. Presence of pancreatic lipase in the duodenal contents demonstrates the proper position of the tube and indicates permeability of the duct of Wirsung except for the possibility of an accessory duct of Santorini.

The intravenous hippuric acid test was suggested for verification of the antitoxic liver function; 1.77 Gm. of sodium benzoate in 20 cc. of distilled water is injected intravenously and normally 0.8 to 1.0 Gm. or more of hippuric acid will be excreted in the urine within an hour, while an excretion of less than 0.7 Gm. would indicate hepatic insufficiency. Normal results are obtained in cholecystitis, cholelithiasis, and calculous obstructions of short standing while insufficiency is encountered in catarrhal jaundice, hepatitis and cirrhosis.

The galactose tolerance test has an equivalent value, except that in cirrhosis it may be impaired by disturbances of the intestinal absorption.

The normal blood cholesterol level ranges between 140 and 220 mg. per cent, of which amount 50 to 70 per cent are represented by esters. Obstructive jaundice generally shows hypercholesterolemia, with a preserved normal ratio between free cholesterol and esters, while in parenchymatous lesions the total cholesterol, and particularly the ester fraction, shows a decrease. Obstructive jaundice shows a parallelism between bilirubinemia and hypercholesterolemia, while in parenchymatous jaundice the bilirubin increases and the cholesterol decreases or remains stationary during the acute phase, and the cholesterol increases and the hyperbilirubinemia tends to decrease during the regenerative phase.

Regulation of the prothrombinemia after parenteral vitamin K administration is a good functional index for the liver; it is present in obstructive jaundice without parenchymatous involvement and the more delayed in parenchymatous jaundice the more severe the process.

Disodium Hydrogen Phosphate Therapy in Lead Poisoning — PROCTOR, CHARLES D. AND KAHN, HARRY S. — *American Journal of the Medical Sciences*, 219: 316 (March) 1950.

Gant proposed the use of disodium hydrogen phosphate ($Na_2HPO_4.7H_2O$) as a therapeutic agent for plumbism. "In expanding this theory, Gant advanced the following advantages of sodium dibasic phosphate: '(*a*) It will precipitate lead in its most insoluble form, the tertiary phosphate ($Pb_3(PO_4)_2$), and apparently this occurs to a large extent in vivo. (*b*) Absorbed lead, and that which is unabsorbed in the gastrointestinal tract, is therefore largely detoxified. (*c*) The slight increase in *p*H (alkalosis) may mobilize some lead previously deposited in the bones. (*d*) Excess sodium ions disturb the calcium balance, calcium and lead being drawn from the trabeculae. (*e*) Mobilization and detoxification occur simultaneously. (*f*) Free ionized lead is diminished by a depression of ionization by the phosphate which is known to be an excellent buffer. (*g*) The salt is also a good cathartic, thus eliminating the use of others.' "

With these postulated advantages in mind the authors undertook a study designed to evaluate this form of therapy on a clinical basis.

"All patients included in this study had clinical symptoms, physical findings or history pointing toward a diagnosis of lead poisoning. These clinical manifestations were also checked by determination of the urinary excretion of lead present in a 24 hour period, using as a criterion for diagnosis of lead exposure the ranges set up by Gant: below 80 micrograms per liter (80 μgm./L), normal; 80 to 150 μgm./L, abnormal exposure; above 150 μgm./L, definite toxicity when accompanied by clinical symptoms. The determinations were made polarographically by one of the authors, the usual precautions against possible contamination having been rigidly observed in the collection of the samples analyzed. Following this confirmation of the diagnosis of lead intoxication, therapy was instituted with disodium hydrogen phosphate heptahydrate, given by either the intravenous or oral route, normal dietary calcium being maintained to guard against hypocalcemia. The course of the patient's progress was followed closely clinically and, in some cases, by repeat analyses of 24 hour urine specimens during the course of the medication. In all cases a polarographic determination on the 24 hour urine specimen was performed at the end of the course of therapy."

Patients with Lead Intoxication.— Case 1: "A 27 year old male complained of anorexia, severe abdominal cramps, and constipation of three weeks' duration. He had worked in a smelting works as a furnace tender for the last three years. A Burtonian line was noted on his gums. Thirty-three stippled cells were found in the blood smears and a 24 hour urine specimen revealed the presence of 500 μgm. of lead per liter. Therapy consisted of 60 grains of sodium dibasic phosphate three times daily by mouth for 15 days. Symptoms disappeared shortly after therapy was started. The 24 hour urine specimen obtained at the end of therapy showed a lead level of 152 μgm./L.

"Case 2: A 52 year old male complained of anorexia, nausea, constipation, abdominal cramps and loss of muscular strength for two weeks. He was a painter by trade. Many basophilic stippled cells were found. The 24 hour urine specimen revealed the presence of 526 μgm. of lead per liter. Therapy consisted of 60 grains of sodium dibasic phosphate orally three times a day for one week. Symptoms had completely disappeared, though the 24 hour urine lead level was 215 μgm./L; therefore treatment was resumed for another week, at the end of which the level had dropped to 138 μgm./L.

"Case 3: A 29 year old male complained of anorexia and constipation of one month's duration. He had been a general laborer in a smelting works for the last two years. Examination of the blood smear showed no basophilic stippling but did show 1.3 per cent reticulocytes. A 24 hour urine specimen revealed the presence of 464 μgm. of lead per liter. Ten grains of sodium dibasic phosphate were given intravenously three times a day for one week. The 24 hour urine lead level dropped from 464 μgm./L to 170 μgm./L. The patient was asymptomatic at this time.

"Case 4: A 45 year old male, who had worked as a brass and aluminum grinder but who had been exposed to the fumes

of melted lead in the foundry in which he worked, complained of severe abdominal cramping pains, anorexia and constipation for one week. A lead line was noted. A moderate normochromic anemia and 63 basophilic stippled cells were present. Five grains of sodium dibasic phosphate were given three times a day intravenously for five days. The pain disappeared the second day and bowel movements returned to normal on the fourth day. The 24 hour urine lead level dropped from 158 μgm./L to 58 μgm./L.

"Case 5: A 67 year old housewife complained of headaches, dizziness, 'spots before her eyes,' anorexia, abdominal cramps and right wrist drop of two months' duration. No lead line was evident, due to adentia. A moderate normochromic anemia and six basophilic stippled cells were present. Five grains of sodium dibasic phosphate three times a day intravenously were given for five days. The symptoms disappeared but the wrist drop persisted. The lead level dropped from 158.4 μgm./L before therapy to 73 μgm./L after therapy.

"Case 6: A 24 year old male, who had worked for six months as a spray painter, complained of anorexia, nausea, vomiting, abdominal cramps, headache and muscular weakness of two weeks' duration. A Burtonian line was present and 21 stippled cells were found in the blood smear. Therapy consisted of 30 grains of sodium dibasic phosphate three times daily for five days by mouth. His symptoms disappeared by the third day. The lead levels were as follows: 190 μgm./L before therapy, 432 μgm. on the second day of therapy, 162 μgm. on the fourth day of therapy and 100 μgm. five days after treatment was completed.

"Case 7: A 48 year old male, a professional spray painter for 10 years, complained of anorexia, nausea, and severe abdominal cramps for one week. No Burtonian line was evident, but a few stippled cells were present. Treatment consisted of 60 grains of sodium dibasic phosphate three times per day orally for five days. The patient was asymptomatic by the fourth day. Lead levels were 163 μgm./L before therapy, 774 μgm. on the fourth day of therapy, and 124 μgm. after treatment was completed.

"Case 8: A 42 year old female had worked at ceramic decorating which involved the use of lead pigment paints for 12 years. She complained of anorexia, dizziness, constipation and peripheral paraesthesias for one month. No Burtonian line was present. Fifteen grains of sodium dibasic phosphate were administered three times daily by mouth for seven days. The patient was asymptomatic after the fourth day of therapy. Lead levels were 128 μgm./L before therapy, 159 μgm. the second day of treatment, and 98 μgm. after the treatment was completed."

The authors were impressed with the value of sodium dibasic phosphate in completely alleviating the clinical symptoms in the above cases of lead intoxication.

"Controls.—Case 1: One of the authors who was completely asymptomatic had an original urinary lead level of 87.2 μgm./L. He had been a spray painter while working his way through medical school seven years previous to this determination. Fifteen grains of sodium dibasic phosphate three times per day orally were administered for five days. The lead levels were as follows: during the first day of therapy, 152.3 μgm./L; the third day of therapy, 45.8 μgm.; and on the fifth day after cessation of therapy, 38.2 μgm. No symptoms were noted at any time during the course of the experiment. Urinalysis remained negative.

"Case 2: The wife of the above author was also asymptomatic and had an original urine lead level of 17.5 μgm./L. Medication was the same as in the above case. On the first day of therapy the lead level was 48.9 μgm./L, on the third day of therapy, 38.2 μgm.; but five days after treatment the lead level was 10.1 μgm. Again no symptoms were noted and the urinalysis remained negative.

"Case 3: The other author, also asymptomatic, had an original lead level of 31 μgm./L. Treatment was the same as in the above 2 cases. On the second day of treatment that level was 135.6 μgm./L and four days after treatment was 25 μgm. Urinalysis again remained negative.

"The results of the 3 control cases appear to demonstrate adequately: (1) that sodium dibasic phosphate is nontoxic; (2) that it markedly increases the excretion of lead in the urine (deleading); and (3) that during the deleading process with markedly increased lead excretion no symptoms were produced."

Pediatrics

Aureomycin in the Treatment of Experimental and Clinical Infections with H. Influenzae, Type B — Chandler, Caroline A. and Hodes, Horace L. — *Pediatrics*, 5: 267 (February) 1950.

"Aureomycin, in doses of 20 mg./Kg. body weight, was as effective in the treatment of mice infected with *H. influenzae,* type B, as streptomycin and dihydrostreptomycin, and more effective than polymyxin or Q-19."

"Because of these suggestive experimental results and because aureomycin has been found to produce essentially no toxic symptoms in man, treatment of patients with *H. influenzae,* type B, infections seemed indicated. To date, 2 patients with *H. influenzae,* type B, meningitis have been treated with aureomycin and sulfadiazine and 3 with aureomycin alone." The following case reports summarize the findings on these patients:

Case 1.—S. C., a 27 month old white male, was admitted to hospital, with the complaint of convulsions and fever of 2 days' duration. Immediately prior to admission, petechiae were noted on the buttocks.

"Past and family histories were noncontributory.

"Patient was well developed and nourished and weighed 15.4 Kg. Face was flushed and he was lethargic but oriented. Temperature was 40° C. There were several petechiae on the buttocks, right wrist and back of the neck. Bilateral otitis media was present. There was an internal squint of the left eye. Tonsils were enlarged and inflamed. There was moderate nuchal rigidity. Kernig's and Brudzinski's reflex signs were positive. No deep reflexes could be elicited except for ankle jerks on the left. Abdominal and cremasteric reflexes were absent.

"Laboratory Examination: Hgb. 11.0 Gm./100 cc., a WBC count of 13.75 thousand/cu. mm. with 73 per cent leukocytes, 24 per cent lymphocytes and 3 per cent monocytes. Urine analysis was negative. Blood culture was positive for *H. influenzae,* type B. Lumbar puncture showed cerebrospinal fluid to be under increased pressure with a white cell count of 7.66 thousand/cu. mm. with 100 per cent leukocytes, a positive Pandy, and only a trace of sugar. The smear showed gram-negative rods that quelled with type B influenzal antiserum. Culture of the spinal fluid was positive for *H. influenzae,* type B.

"On admission, the patient was given Na-sulfadiazine 750 mg. and aureomycin 50 mg. intravenously, and aureomycin 125 mg. by mouth. Thereafter, he was given a daily dosage of aureomycin 100 mg. intravenously for 6 days, and aureomycin 750 mg. orally for 13 days, making a combined total dosage of 10.35 Gm. The total dose of sulfadiazine given was 14.25 Gm. Within 24 hours after the institution of therapy, the temperature reached normal and the meningeal signs became less marked, but an internal squint developed on the right. Culture of the spinal fluid was still positive for *H. influenzae* on the day after admission, but thereafter remained negative until discharge. Except for an occasional slight elevation of temperature during the first week of his hospital stay, the patient made an uneventful convalescence and was discharged after 3 weeks as fully recovered. Aureomycin was well tolerated with no signs of toxicity."

Case 2.—L. M., a 16 month old white female, was admitted to hospital with the diagnosis of meningitis. "Twelve days prior to admission, she developed fever, listlessness and rapid breathing. A diagnosis of pneumonia was made and penicillin therapy was begun. Treatment was continued until 6 days prior to admission. On the night before admission, she developed stiffness of the neck and screamed whenever she was moved." On the day of admission a lumbar puncture was done. "A tentative diagnosis of *H. influenzae* meningitis was made on the basis of a smear of the cerebrospinal fluid and she was given penicillin 5,000 units and streptomycin 25 mg. intrathecally stat." She was then transferred to another hospital. "Past and family histories were noncontributory.

"Patient was well developed and nourished and weighed 9.1 Kg. She looked moderately ill, and held her head stiffly. Temperature was 40.3° C. Anterior fontanel was firm. Neck was resistant to anterior flexion. There was slight impairment of resonance with diminished breath sounds over the base of the right lung. There was a soft systolic murmer at the apex and along the left sternal border. Liver edge was palpable 2 fingerbreadths below the costal margin. All reflexes except the knee jerks were present. Kernig's and Brudzinski's reflex signs were negative. The cranial nerves appeared to be intact.

"Laboratory Examination: Hgb. 10.0 Gm./100 cc., WBC count 22.4 thousand/cu. mm. with 73 per cent leukocytes, 23 per cent lymphocytes and 4 per cent monocytes. Urine analysis was negative. Blood culture was positive for *H. influenzae*, type B. Culture of the nasopharynx was positive for pneumococcus, type 14. Lumbar puncture showed the cerebrospinal fluid to be milky with a white cell count of 1.2 thousand/cu. mm. with a positive Pandy and no sugar. The smear showed gram-negative bacilli that quelled with type B influenzal antiserum. Culture of the spinal fluid was positive for *H. influenzae,* type B.

"On admission, patient was given aureomycin 50 mg. and Na-sulfadiazine 500 mg. intravenously, and aureomycin 125 mg. by mouth. Thereafter, she received a daily dosage of aureomycin 100 mg. intravenously for 6 days, and aureomycin 500 mg. orally for 14.5 days, making a combined total dosage of 7.85 Gm. Total dose of sulfadiazine given was 24.25 Gm. Within 24 hours after the institution of therapy, temperature reached normal and the patient continued to be afebrile throughout the rest of her hospital stay. Both blood and spinal fluid cultures became negative on the day after admission and remained negative thereafter. All meningeal signs disappeared within 72 hours and at discharge the patient had made a complete recovery with no signs of residual damage. There were no evidences of drug toxicity at any time."

Case 3.—F. L., a 2 ½ year old Negro female, was admitted to hospital, with the diagnosis of *H. influenzae* meningitis.

"Past and family histories were noncontributory.

"Nine days prior to admission, she developed fever, anorexia and wheezy breathing. She was given sulfadiazine 1 ½ Gm. daily for 3 days. Temperature fell to normal and she seemed essentially recovered until the evening before admission when her temperature rose to 38.3° C. and her neck seemed stiff." On the morning of admission a lumbar puncture was performed. "A smear of the spinal fluid showed gram-negative rods which quelled with *H. influenzae,* type B, antiserum." She was transferred to another hospital.

"Patient was well developed and nourished in no acute distress. She was irritable and resisted being moved, but was otherwise alert and cooperative. Temperature was 39.6° C. There was marked nuchal rigidity. All reflexes were hyperactive. Brudzinski's, Kernig's and Babinski's reflex signs were negative.

"Laboratory Examination: Hgb. 9.0 Gm./100 cc., WBC count of 13.4 thousand/cu. mm. with 96 per cent leukocytes and 4 per cent monocytes. Urine analysis was negative except for a 3+ acetone. Blood culture was negative for *H. influenzae*, type B. Lumbar puncture showed the cerebrospinal fluid to be slightly cloudy with a white cell count of 700/cu. mm. with 80 per cent leukocytes, a positive Pandy, and a moderate decrease in the sugar content. The smear showed gram-negative rods that quelled with type B influenzal antiserum. Culture of the spinal fluid was positive for *H. influenzae,* type B. In vitro, the growth of this organism was inhibited by aureomycin 0.6 μgm./cc. broth.

"On admission, patient was given aureomycin 50 mg. intravenously and 125 mg. by mouth. Thereafter, she was given a daily dosage of aureomycin 140 mg. intravenously for 9 days and 750 mg. orally for 14 days, making a combined total dosage of 12.9 Gm. Although she showed marked clinical improvement within 24 hours, cultures of her spinal fluid remained positive for 6 days after therapy was instituted. The level of aureomycin in the spinal fluid was determined on three separate occasions during this period and was found to range from 0.1 to 0.4 μgm./cc.

"Determinations of the susceptibility of the *H. influenzae* isolated from the spinal fluid on 5 successive days showed that the organism continued to be inhibited by aureomycin 0.6 μgm./cc. broth.

"Patient's temperature, which fell initially from 40° C. to 37.3° C. within 24 hours after the institution of therapy, continued to spike to around 38.3° C. for the first week in the hospital. Thereafter, she remained afebrile and progressed rapidly to complete recovery. Except for the vomiting of two oral doses of aureomycin when therapy was first begun, there were no evidences of drug toxicity."

Case 4.—R. B., a 2 year old white male, was admitted to hospital with the diagnosis of meningitis.

"Past and family histories were noncontributory.

"Forty-eight hours prior to admission, he was seen by a physician because of vomiting and a temperature of 40° C. He was given penicillin and a sulfonamide was also prescribed. The next day, he was given more penicillin, but vomiting and fever continued. On the morning of admission, his condition was unchanged and, in addition, his neck was stiff." A diagnosis of meningitis was made.

"Patient was well developed and nourished and weighed 10.4 Kg. He was lethargic but did not appear to be critically ill. The temperature was 38.1° C. Neck was resistant to anterior flexion. Deep reflexes were equal but hyperactive. Abdominal reflexes were hyperactive, Babinski's reflex signs were negative.

"Laboratory Examination: Hgb. 5.5 Gm./100 cc., WBC count of 13.32 thousand/cu. mm. with 56 per cent leukocytes, 41 per cent lymphocytes, and 3 per cent monocytes. Urine analysis was negative except for a trace of acetone. Blood culture was negative. Lumbar puncture showed the cerebrospinal fluid to be cloudy with a white cell count of 3.48 thousand/cu. mm. with 98 per cent leukocytes, a positive Pandy, and traces of sugar. The smear showed gram-negative bacilli that quelled with type B influenzal antiserum. Culture of the spinal fluid was positive for *H. influenzae,* type B. In vitro, the growth of this organism was inhibited by aureomycin 0.6 μgm./cc. broth.

"On admission, the patient was given aureomycin 50 mg. intravenously and 125 mg. by mouth. Thereafter, he received a daily dosage of aureomycin 100 mg. intravenously for 6 days, and 500 mg. orally for 16 days, making a combined total dosage of 8.75 Gm. On the day after therapy was instituted, cultures of the spinal fluid became negative and remained negative throughout the patient's course in the hospital. Temperature fell to normal within 24 hours but rose intermittently to 38.3° and 38.8° C. for the next 4 days. Thereafter, the patient remained afebrile and progressed rapidly to complete recovery. There were no evidences of drug toxicity at any time."

Case 5.—E. W., a 6 year old Negro female, was admitted to hospital, with the diagnosis of influenzal meningitis.

"Past and family histories were noncontributory.

"Forty-eight hours before admission, she was seen by a physician because of vomiting and listlessness. Penicillin and sulfonamides were prescribed by mouth. On the day prior to admission, she became irrational and ran a high fever." On the day of admission, a diagnosis of *H. influenzae* meningitis was made. She was then transferred to another hospital.

"Patient was slender, asthenic and appeared acutely ill and sluggish. Temperature was 40° C. Eyes responded sluggishly to light. Neck was markedly resistant to flexion. Breath sounds were slightly suppressed over the entire right lung. Deep reflexes and the abdominal reflexes could not be elicited. Babinski's reflex signs were negative.

"Laboratory Examination: Hgb. 12.0 Gm./100 cc., WBC count of 24 thousand/cu. mm. with 84 per cent leukocytes, 12 per cent lymphocytes and 4 per cent monocytes. Urine analysis showed acetone to be present, but was otherwise negative. Blood culture was positive for *H. influenzae,* type B. Lumbar puncture showed spinal fluid to be cloudy with a white cell count of 24 thousand/cu. mm., a positive Pandy, and a complete absence of sugar. Smear showed gram-negative bacilli that quelled with type B influenzal antiserum. Culture of the spinal fluid was positive for *H. influenzae,* type B.

"On admission, the patient was given aureomycin 75 mg. intravenously and 200 mg. orally. Thereafter, she received a daily dosage of 150 mg. intravenously for 5 days and 800 mg. orally for 14 days, making a combined total dosage of 21.5 Gm. On the day after therapy was instituted, spinal fluid cultures became negative and remained negative on further culturing. Blood culture taken on the fourth day after admission was negative. Temperature fell to normal within 24 hours and, except for a transient rise on the fourth day, remained normal throughout. Patient made a full recovery. There were no toxic drug reactions."

There was an additional patient with *H. influenzae* meningitis who was treated with aureomycin and sulfadiazine in whom the outcome was fatal. "This patient was a 4 ½ year old white male who was admitted to the hospital in a moribund condition after an illness of only 13 hours' duration. He was given aureomycin 75 mg. intravenously every 12 hours and aureomycin 250 mg. by rectum every 6 hours together with large doses of sulfadiazine intravenously and subcutaneously. In spite of this therapy, patient never regained consciousness and died 36 hours after admission. Spinal fluid cultures of the initial lumbar puncture and one performed 24 hours after admission were positive for *H. influenzae*, type B, but the postmortem spinal fluid culture was sterile. The postmortem blood culture was also sterile."

Encephalitis Following Vaccination Against Pertussis — EDITORIAL — *Annals of Internal Medicine*, 32: 343 (February) 1950.

"Severe injury of the brain ('encephalitis') and spinal cord has been observed as an immediate or early sequel of many immunization procedures, including the inoculation of living vaccines, killed bacterial suspensions or other culture materials, and prophylactic antiserums. . . . Encephalitis may also occur as a sequel of vaccinia. . . . It occurs chiefly in older children and young adults after the first vaccination, practically never in infants. Partly for this reason it is relatively rare in the United States.

"The symptoms are characteristic and appear 10 to 12 days after vaccination, at the height of the cutaneous eruption. The onset is abrupt with fever, malaise, headache, pain in the back, vomiting and drowsiness. This progresses rapidly to coma, often in association with convulsions, accompanied by flaccid paralyses of the legs, loss of reflexes, frequently bulbar palsy, and other evidences of focal brain injury. Death occurs in about 50 per cent of the cases, usually after five or six days, but those who survive usually recover completely or nearly so. The pathogenesis of this disturbance is also still uncertain.

"Recent observations indicate that grave injury to the nervous system with symptoms resembling those described in postvaccinal encephalitis may follow the administration of pertussis vaccine. Several observers over the past 15 years, in reports concerned primarily with the effectiveness of the vaccination, have mentioned or described isolated instances of such reactions. . . . The manifestations were quite similar in most of the cases, and they constitute a clearcut clinical syndrome.

"The age of the children affected ranged from 6 to 18 months at the time of the vaccination, and 12 of the 15 were males. The children were regarded as normal before the vaccination, and in none had convulsions been observed. The usual dose of fluid vaccine was given in 12 cases, and in the others it was combined with diphtheria or tetanus toxoid or both.

"Symptoms appeared after an interval of from 20 minutes to 72 hours following the injection, in 12 cases within 12 hours. The onset was usually abrupt with high fever, restlessness, irritability or drowsiness, followed quickly by generalized or occasionally unilateral convulsions and coma. Usually there were evidences of gross organic cerebral lesions. These included hemiplegia or hemiparesis in several, and generalized spasticity with exaggerated reflexes and positive Babinski sign. In 1 case . . . . the third severe reaction to successive injections of vaccine was followed by a persisting generalized flaccid paralysis including bulbar palsy and weakness of the sphincters, and death from pneumonia occurred seven weeks later.

"All 15 cases of Byers and Moll survived the acute illness which subsided after 2 to 10 days. Two subsequently died of pneumonia in other institutions after periods of progressive deterioration of 6 and 18 months, respectively. At autopsy in 1 of these, 'diffuse atrophy and gliosis of the brain' were found.

"Subsequent examination of these cases showed reasonably satisfactory recovery in only 1. In 3 instances, the interval was too short to warrant final conclusions, but in the 9 others there were serious and almost certainly permanent sequelae of varying severity. Of the 13 surviving children, recurrent convulsions persisted in 9. Cerebral palsies were present in 7, 2 of whom were blind. Two were 'virtually decerebrate.' Four of these had walked before their illness. Six showed mental retardation, and 1 of these, in addition to the 2 fatal cases, was grossly defective. The electroencephalograms (in 12 cases) showed gross abnormalities in 4, slowed rhythm in 4 and were regarded as normal in 4. Pneumoencephalograms in 10 cases showed borderline normal records in 2 and abnormalities in 8, including dilatation of one or both lateral ventricles. In several these were marked and indicated severe cortical atrophy."

In an effort to determine the frequency of such reactions, a questionnaire was circulated asking specifically regarding the occurrence of convulsions after pertussis vaccination. Reports were obtained of "at least 38 authentic cases" from 17 different sources. "There were 2 deaths." Twelve cases are said to have shown "irreversible changes." "Twenty-three were said to have recovered completely. Although investigations of this type are unsatisfactory in many respects, this does in general confirm the observations of Byers and Moll."

"Byers and Moll reported that in the 10 year period during which their 15 cases had occurred, 8 cases of postvaccinal encephalitis had been admitted to the Children's Hospital and 28 cases of 'encephalitis' complicating an attack of pertussis had been observed. Since vaccination against smallpox presumably was carried out in a larger proportion of the population than the administration of pertussis vaccine, the incidence of encephalitis following the latter in that area seems to have been more than double that of postvaccinal encephalitis and fully equal to that of the encephalitis occurring spontaneously during an attack of pertussis."

"The pathogenesis of this encephalitis has been the subject of much speculation, but it is still not established. It is not due to contaminated or faulty vaccine. Some have suggested that it is due to the action of specific bacterial toxins contained in the vaccine. The formation of toxins by *Hemophilus pertussis* has been demonstrated, but these are extremely unstable substances, and it seems unlikely that they could retain their activity in the vaccine for any significant period of time. Autopsy material is too scanty to warrant any conclusions, although the little available suggests a toxic or degenerative process rather than a local infection.

"There are many analogies between this condition and the encephalitis following vaccinia, rabies vaccine, and that occurring rarely during such infections as variola, varicella, rubella and rubeola. The pathogenesis of the neurological lesions in these diseases, however, is also uncertain. One might expect that in these infections there was an unusual localization of the virus in the brain. The tissues have been studied in a considerable number of cases, but there is a sharp difference of opinion among pathologists as to whether the lesions are primarily inflammatory or degenerative. Most of the cases have shown some degree of perivascular infiltration of lymphocytes, usually slight or moderate, as well as degenerative changes in the nerve cells of varying severity and extent. The most characteristic feature, which is common to all of these conditions, is the occurrence of perivascular areas of demyelinization, especially about the smaller veins, with little or no infiltration with lymphocytes. Many phagocytes stuffed with fat droplets are usually present, but these are largely of the gitter cell type and are believed to be derived from neuroglia. These lesions resemble those found in multiple sclerosis and acute disseminated encephalomyelitis, which are regarded by many investigators as primarily degenerative processes. The lesions differ from those in such infections as poliomyelitis and epidemic encephalitis, in which the nervous tissue is directly invaded by the virus and in which there is

marked perivascular infiltration with lymphocytes but no such foci of demyelinization."

"The close similarity of the encephalitic lesions in all of these conditions, vaccina, antirabies vaccination, variola, varicella, measles, suggests although it does not prove that the same mechanism is involved in the production of all of them. This has led to the suggestion that they are caused by some unrelated virus which had been present in the individual in a latent state and was activated by the vaccination or the infection." This view is purely speculative.

"The rarity of such attacks strongly suggests that, whatever the mechanism, they must depend in part upon some individual peculiarity or predisposition. The view that they are the result of a local allergic reaction (antigen-antibody reaction) has been supported. . . . The appearance of encephalitis in variola, measles and vaccinia is usually on the tenth to fourteenth day, when the local reaction is at its height and the development of hypersensitiveness is to be anticipated.

"In these cases as well as those showing encephalitis after pertussis vaccine, manifestations of a generalized anaphylactic reaction are unusual, and one must assume a localized reaction in which the brain functions as the shock organ."

"In the cases of encephalitis following pertussis vaccine, the symptoms have usually appeared within a few hours, and previous sensitization must be assumed." Opportunity for this is obvious in cases in which the encephalitis followed the second or third injection, but in 6 of the cases of Byers and Moll and in several collected by another writer, it followed the initial dose. "Although a previous unrecognized attack of pertussis can not be absolutely excluded, it is unlikely that this had occurred in all of these cases. In the cases of horse serum, however, many of the fatal reactions have followed the first injection of antitoxin, and it must be recognized that occasional individuals can become highly sensitive to substances with which they apparently have had no previous contact.

"There is evidence in some of these cases that hypersensitiveness is increased by the injection of vaccine. In 2 of Byers and Moll's cases, a fairly severe reaction (but without neurological manifestations) had followed the preceding injection of vaccine." In 3 of their cases and in 2 of another writer, in spite of severe reactions with evidence of brain injury, subsequent injections of vaccine were nevertheless given, and all were followed by reactions of even greater violence. "In 2 cases negative local reactions were reported following subsequent intradermal injections of pertussis vaccine to test for hypersensitiveness." In another case this was followed immediately by a severe exacerbation of the neurological disturbances.

"Similar reactions with manifestations of encephalomyelitis have been observed in rare instances after injections of foreign protein of other types; e.g., horse serum, coli-streptococcus vaccine, and typhoid vaccine.

"Although the evidence is not conclusive, it seems probable that the encephalitis following pertussis vaccine is due to a local allergic (antigen-antibody) reaction. The same may well be true of the cases associated with smallpox and rabies vaccine and the viral infections. The similarity of the pathologic lesions in the brain, however, is not adequate proof that the same etiologic factor is concerned in all of them.

"One may conclude that the administration of pertussis vaccine involves a definite but remote risk of causing a damaging encephalitis. It is comparable in its incidence to that of the encephalitis following smallpox vaccination; its immediate mortality has been less, but the frequency of severe permanent injury to the brain has been higher. The mortality of pertussis in young children is so high, however, and the protective value of the vaccine so well established that the remote risk of encephalitis should not interfere with the widespread use of the vaccine.

"Certain precautionary measures, however, are definitely indicated. All cases should be observed following administration of the vaccine and further doses withheld if severe reactions occur and particularly if there are convulsions or any other reasons to suspect cerebral injury. As a rule it should not be given to children with fever or other evidence of acute illness. It seems prudent to use special caution in cases with evidence of cerebral damage of other types and in those who

have shown manifestations of hypersensitive reactions, although there is as yet no direct evidence that encephalitis has occurred more frequently in either group. It is also important that all such reactions be observed and recorded, so as to furnish more precise information as to their incidence, their nature, and the existence of possible predisposing factors."

The Problem of Average Childhood Alimentation — SÁENZ HERRERA, CARLOS — *Boletín del Instituto internacional americano de protección a la infancia,* 23: 346 (December) 1949.

Alimentation of infants is not a serious problem in Costa Rica as most infants receive breast feeding. An average of 500 to 600 calories daily is needed during the first year of life, and as 75 per cent are furnished by milk 600 to 700 Gm. of milk daily are required. About 18 Gm. of proteins daily are required, and this amount is furnished by 500 Gm. of milk. The carbohydrate requirements are covered in natural alimentation but cow's milk requires supplementation by sugar or cereals. The fat concentration of milk varies but a 3.5 to 4.0 per cent fat concentration is satisfactory. Vitamins and minerals are present in acceptable quantities in fruit juices, cod liver oil and some vegetables which are suitable for babies above the age of 5 months. In some areas of Costa Rica, milk is difficult to obtain in a fresh form and expensive and there the government has to solve the problem of lack of equilibrium of nutritional sources.

During the second year of life the child needs an average of 80 calories per Kg. body weight, that is 750 to 850 calories per day, with 20 to 25 Gm. of protein. About half of the calories and the protein may be obtained from milk, while meat and eggs will furnish supplementary protein; bread, cereals, fruits and vegetables will complete the diet. In the author's hospital experience, nutritional deficiencies are much more frequently encountered during the second year of life than during the first year of life.

The deficiency states are of particular significance during the preschool age, between the ages of 2 and 6; intestinal parasites and other affections have more serious repercussions in nutritional deficiency, and normal growth is interfered with if not enough plastic material is available. About 80 calories per Kg. or a total of 800 to 1,400 calories are required, with 30 to 50 Gm. of protein, chiefly of animal origin. The usual diet in Costa Rica is low in protein and fat and almost exclusively based on carbohydrates; in preschool children such a diet leads to multiple deficiencies.

In school children the diet may resemble that of the adult and throughout the period of active growth 70 to 80 calories per Kg. body weight are required. The protein requirements amount to 1.8 to 2.8 Gm. per Kg. body weight, and should be supplied by animal and vegetal foods in a ratio of 2 to 3. At the age of 10 the average weight is 30 Kg. and the daily requirements amount to 2,100 to 2,400 calories, with 80 Gm. of protein. According to one writer, a school child needs 75 per cent of the adult requirements.

In spite of their lesser weight adolescents have a caloric requirement similar to that of the adult, and the protein supply should amount to 90 Gm. The cost for feeding of infants is $0.40 daily with natural feeding and $0.80 with artificial feeding; that during the second year of life is $0.80 to $1.00, that for preschool children $0.80, that for school children $1.00 to $1.20 and for adolescents $1.65.

The nutritional problem differs in different parts of Costa Rica; the incidence of nutritional deficiencies is lower where the milk consumption is high, and where milk consumption is low powdered milk and cheese should be used in order to balance the almost exclusive carbohydrate diet. It has been shown that the severity of the syndrome of ancylostomiasis is linked to the meat consumption and the latter should be increased where infestation is heavy.

The schools should play an important part in an intense educational campaign which is needed for the spread of better knowledge of nutritional facts. Intestinal parasites and malaria should be combated with all hygienic measures available.

The deficiency problem in Costa Rica is essentially one of protein deficit and the consumption of protein should be increased in order to diminish the incidence of de-

ficiency conditions; the soy bean should be of great value in this direction. In the author's opinion the economical factor is of greater importance than the cultural one; more than half of his cases of deficiency states come from homes where the income per person is only 34 cents for meals. In addition, ignorance, poor hygienic conditions, intestinal parasites and alcoholism play a part. Relapses of nutritional deficiency states are extremely frequent after return to the original environment, and only a rising living standard of the population at large will lead to real improvement of these conditions.

Acute Conjunctivitis Caused by Hemophilus — DAVIS, DORLAND J. AND PITTMAN, MARGARET — *American Journal of Diseases of Children*, 79: 211 (February) 1950.

A severe form of acute conjunctivitis was observed in the lower Rio Grande Valley of Texas. "Infants and children were attacked more commonly than adults, and there was a high familial incidence. The principal cause of the infection was the Koch-Weeks bacillus, although a number of attacks were caused by *Hemophilus influenzae*."

The disease begins with watering and irritation of one eye, usually followed in a few hours by vascular injection of the conjunctiva, and pain. "The discharge soon becomes purulent, and the lids are often tightly adherent with dried exudate when the patient awakes in the morning. On the second or third day, the lids may become edematous and in severe attacks they are so swollen that the patient has difficulty in opening them. In many patients the other eye becomes involved a day or two after the original eye is affected. Usually, the conjunctivas are severely inflamed, and there may be ecchymoses of the bulbar conjunctivas. Photophobia, pain and tenderness are prominent features at this stage, and phlyctenules may appear on the cornea. However, most attacks do not progress to this degree of severity and all gradations of the disease may be seen, including mild conditions with only slight vascular injection and irritation lasting a few days. Rarely is there enlargement or tenderness of the preauricular lymph nodes. Many patients, particularly children, show a slight elevation of temperature of 1 to 2 degrees (F.). There appears to be no sequelae, and the signs and symptoms gradually regress over a period of several weeks in untreated patients."

"One attack appeared to confer little, if any, protection against later attacks, since approximately 16 per cent of 118 patients for whom data were available were reported as having had a previous attack within six months. Some children had recurrent attacks every month for a period of several months.

"The disease was reported by physicians to be commonest during the warm months of the year, particularly the early fall, and was seen in both urban and rural areas. Immigrant Mexican agricultural workers were heavily attacked, and the disease assumed great importance as a cause of absence from school and work.

"The exact means of transmission of the disease is not known, but many physicians and others are of the opinion that the eye gnat, *Hippelates pusio*, may serve as a vector of the causative agent. These gnats are particularly abundant during the warm months and are attracted by the moist mucous membranes of man or animals. They are frequently seen clustered about the eyes of infants, particularly if exudate is present. Gnats could act as a mechanical means of transfer, but their importance, if established, would have to be evaluated in relation to transmission of infectious material by fingers, clothing, towels, or other fomes."

In experimental human infections treatment with streptomycin appeared to be beneficial. Therefore, an investigation was undertaken to observe therapeutic results in naturally occurring infections under clinical conditions. For this part of the study 73 patients with the complaint of "sore eyes" were examined, brief histories recorded and conjunctival cultures taken. "Some patients were treated with streptomycin, and others were treated with zinc sulfate U. S. P. as basis of comparison with the streptomycin therapy.

"Streptomycin was applied as a 0.1 per cent solution in 0.85 per cent sodium chloride solution either with an eye cup or, in infants, with an eye dropper. Some patients were treated with 0.5 per cent

streptomycin ophthalmic ointment. Zinc sulfate was used as a 0.25 per cent solution in an eye cup or by dropper. After the initial treatment, all patients possible were kept at the clinic and treated again two hours later; then four hours later cultures were made and the patients were treated again. The patient, or the parents, was provided with the medicament and instructed to continue treatment at home every two hours and to return on successive days for observation and reculture. Therapy was continued for three days, then stopped completely.

"Sixty of these 73 persons were observed subsequently, and in all but 3 there was definite clinical improvement. For 30 patients either the Koch-Weeks bacillus or *H. influenzae* was isolated from the culture material taken preceding treatment, and in each patient the effect of treatment was followed by cultures. . . . The Koch-Weeks bacillus was originally isolated from 20 patients and *H. influenzae* from 10.

"Twenty-two patients were treated with streptomycin and 8 were treated with zinc sulfate. They ranged in age from 3 months to 12 years, and one half of them had had the infection four days or less. Among the remainder, 5 had had the disease for a month or longer. . . . Cultures taken four hours after treatment were positive in only 2 of 8 children treated with streptomycin for whom cultures were made and in 3 of 6 treated with zinc sulfate for whom cultures were made. At 24 hours, 2 of 12 treated with streptomycin and none of the 8 treated with zinc sulfate had positive cultures when they were examined. After 48 hours or more, only 1 child, a cachectic 3 month old infant with a severe infection of the upper respiratory tract, still harbored *H. influenzae* in the conjunctiva."

While the treatment schedules appeared to be beneficial, the writers did not determine whether other methods or regimens of application of streptomycin or zinc sulfate would be as effective or less so. However, their observations impressed them with the importance of proper administration of either drug so that a sufficient concentration reaches the infected conjunctiva for an adequate length of time. "In persons with conjunctivitis with concurrent infection of the upper respiratory tract there is the possibility of reinfection after treatment. . . . Clinical improvement was manifested by diminished conjunctival exudate and secretion and reduced pain, then later by lessened vascular injection. In some patients the improvement appeared as early as four hours after treatment was started.

"In the vicinity of Washington, D. C., a number of patients with acute conjunctivitis have been observed during the late winter months. From 9 of these persons, including 3 adults and 6 children under 5 years old, nontype-specific *H. influenzae* was recovered in almost pure culture. In nearly every one of these patients the conjunctivitis was preceded by an infection of the upper respiratory tract which persisted during the ocular infection. The response to streptomycin therapy was prompt, though several of the infections tended to recur about seven days later, but then promptly cleared with further streptomycin treatment."

Acute, Subacute and Chronic Primary Atypical Virus Pneumonia — KEIZER, D. P. R. — *Pediatrie*, 39: 105, 1950.

Primary atypical pneumonia, also termed atypical abacterial, acute, grippal or interstitial pneumonitis is epidemic in Holland and its pathologic aspects are well established. Although it seems to spread like a new disease an old affection can be recognized in it, and the Army Medical Museum has lung specimens from soldiers who died during the Civil War which closely resemble the findings of present day fatal cases. The main difficulty of a study of atypical virus pneumonia is caused by the impossibility of cultivating the active virus; other atypical abacterial pneumonias are known, like ornithosis and Q fever, and have been transmitted to volunteers with water from throat lavages of patients.

Periarteritis nodosa, blood eosinophilia, tuberculosis, pulmonary mycoses and sulfonamide allergy may produce roentgenologic pictures identical with those of atypical pneumonia. Interstitial plasmocytic pneumonia, a serious affection of prematures and infants, is a completely different affection.

Atypical pneumonia may occur in tropical countries but most reports come from

temperate climates. The mortality rate is low and therefore only relatively few autopsy reports are available. One writer published 44 autopsies and mentioned that the pneumonic foci did not respect the lobar boundaries; the infected pulmonary areas are not as dense as in acute lobar pneumonia and less well separated from healthy areas. Other lesions include peribronchitis, interstitial pneumonitis, acute bronchiolitis with pus and mucus, desquamative phenomena, very few germs, bronchiolar enlargement, and scattered mononuclear elements in the interalveolar walls. Hyaline membranes and fibrin threads may be encountered. The bronchial epithelium is almost always intact, and inclusions, elementary bodies and Rickettsiae are always lacking.

The onset of atypical pneumonia is not as sudden as that of lobar pneumonia, and chronic cases are observed. The temperature is moderately elevated; bradycardia has been reported but was present in only 1 of the author's cases. The history usually shows chronic complaints like stubborn cough, diarrhea, loss of weight, anorexia and vague pains; if the onset is more sudden it is marked by profuse expectoration rich in mucus, retrosternal, muscular and articular pains, and less dyspnea than in lobar pneumonia. Cyanosis and herpes are often absent. There is a striking discordance between physical signs and roentgenologic findings. The roentgenogram may reveal atelectasis or veiling, particularly of the lower lobes, with pleural thickening. The symptoms may persist for two to six weeks before the peribronchitic foci are absorbed from the periphery to the hilus. The author has observed cases in which the roentgenologic signs persisted unchanged for 6 to 18 months, with positive serologic signs.

The blood picture shows moderate leukocytes and the sedimentation rate is slightly elevated. The author could not confirm the reports that nonspecific syphilitic reactions are produced, probably because the examinations were done too late. Cold agglutination supervenes after a few weeks while the syphilitic serologic reactions are an early sign. Cold agglutination of group O erythrocytes with dilutions of the patient's serum is diagnostically helpful; it is not specific and may be encountered in trypanosomiasis, paroxysmal hemoglobinuria and hepatic affections but the high titers found in atypical pneumonia are unknown in grippe, ornithosis, Q fever, acute adenolymphitis and other affections. The author considers a titer of 1:32 as positive, if it increases during the course of the disease, but a negative cold agglutination does not rule out atypical pneumonia. Cure with negativization of the agglutination test is the rule, and disappearance of the clinical symptoms with persistent cold agglutination test suggests other localizations, as in the maxillary sinuses or the lymph glands.

The incubation period is said to range between 2 and 21 days but is difficult to determine because of the vague character of the premonitory symptoms. A certain degree of contagiosity is present, and among his 120 cases of which 91 were observed clinically, the author found several instances of multiple cases in one family.

It is difficult to decide whether atypical pneumonia is susceptible to recurrences or not; as long as the cold agglutination test persists there is the possibility that the patient is not cured, and without consideration of the curve of the cold agglutination titer one cannot speak of new infections or recurrences. It seems wise to maintain that atypical pneumonia presents periods of exacerbation and clinical silence linked by persistence of the cold agglutination test, until true cure supervenes. Acquired immunity is difficult to prove. The persistent cold agglutination test after atypical pneumonia seems analogous to the persistent Paul-Bunnell test in infectious mononucleosis, and in both affections the number of observations of chronic cases is increasing.

Abacterial pneumonias do not respond to sulfonamide treatment; atypical pneumonia may provoke serious anemia and sulfonamide treatment may aggravate the anemia. Penicillin is ineffective against the virus but cures secondary bacterial complications. Streptomycin treatment may be effective, depending on the nature of secondary bacillary infections, and is effective in cases in which the atypical pneumonia aggravates a primary tuberculous infection. Only aureomycin is capable of immediate control of the infection; the author's ex-

perience with this drug is limited to 3 cases but in 1 of them spectacular cure was achieved within three days while the patient had been moribund from atypical pneumonia on institution of the treatment, definitely indicating an etiologic therapeutic effect. In cases with complicating meningocerebrocerebellar symptoms, particularly in small children, the author used gamma globulin with definite success, but relapses could not be prevented. Otherwise treatment is symptomatic; bed rest is indicated for a certain period of time, and a stay at the seashore is advantageous. The patients must be followed up after apparent cure as virus pneumonia may lead to bronchiectases, pulmonary cirrhosis, and perhaps constrictive pericarditis. Serious complications of virus pneumonia include cardiac, neurologic, urinary, otogenic, hepatic and suprarenal ones.

The author observed clinically 41 boys and 55 girls up to the age of 13 with virus pneumonia; the cold agglutination test was positive in 36 boys and 45 girls. Young children and infants were included in large numbers. The right lung was more frequently involved than the left one. The leukocytosis was much less marked than in bacterial pneumonia. The sedimentation rate was found to be slightly elevated. Blood and spinal fluid cultures were always negative. Even in cases with neurologic complications and a high blood titer of cold agglutinins no such agglutinins could be demonstrated in the spinal fluid. No virus could be cultured from sputum or spinal fluid. Whenever possible contact with sick animals and the possibility of ornithosis and Q fever was ruled out. In several cases the pneumonia started with a scarlatiniform or rubeoliform rash, and a Dick test and an accurate blood examination is required to rule out eruptive fevers. Remarkably a similar rash may be encountered in infectious mononucleosis. In 2 cases the author observed an acute strophulus; this seems interesting as 1 claimed a viral nature of strophulus. Atypical pneumonia may provoke strophulus in predisposed children without being its true cause. Several children had experienced measles, grippe or whooping cough before the atypical pneumonia; the latter may be contracted before or after the usual infectious diseases and a diminished resistance may be assumed. None of the affections mentioned gives a high titer cold agglutination test. The Paul-Bunnell test was negative in all cases except those of mixed infection. Two patients showed generalized lymphadenitis; histologically only benign reticulosis was found and neither serologic nor morphologic examinations proved infectious mononucleosis so that in these cases pseudomononucleosis must be assumed. In some cases of atypical pneumonia the cold agglutination test was negative, and if in such cases other family members contracted the disease they, too, showed a negative test. Complications in the author's 96 cases included 2 cases of veiling of the maxillary sinus, 8 of severe anemia, 4 of exudative pleurisy, 7 of dermatologic processes, 5 of acute hepatitis with jaundice, 5 of acute nephritis, 9 of neurologic syndromes, 2 of cardiac syndromes, 5 of corticosuprarenal insufficiency, 3 of acute mastoiditis, and 5 of chronic enteritis. Two patients showed beginning bronchiectasis formation and 1 pulmonary cirrhosis. Two children had a primary tuberculous infection. One girl aged 8 was operated upon for bronchiectasis, and contracted a severe atypical pneumonia at home improved by gamma globulin; she developed acute hepatitis with jaundice and subsequently the condition remained unchanged and active tuberculosis was found, with bacilli in the gastric juice. The condition became serious but was controlled by streptomycin treatment. The second case concerned an infant, aged 6 months, who had been vaccinated perorally with BCG; this infant developed atypical pneumonia with subcutaneous tuberculous infiltration at the left mandible, with caseation, calcification and giant cells. After cure of the atypical pneumonia signs of bronchiectasis became noticeable. The nervous complications were represented by encephalopathies with or without hemiplegia, cerebellar ataxia, abacterial meningitis, and a diencephalic syndrome with obesity. One boy aged 5, developed an acute viral myocarditis and was cured by a blood transfusion from his father who had atypical pneumonia. One boy with atypical pneumonia developed acute endocarditis and hemorrhagic nephritis but was taken home before complete cure.

Treatment of Malaria in Children with Chloroquine — NELSON, THOMAS L. AND CONLIN, GERALD J. — *Pediatrics*, 5: 224 (February) 1950.

"Fifty-four consecutive cases of malaria in children ranging in age from 8 months to 12 years with an average age of 4.9 years, were treated with chloroquine diphosphate. Of these 54 cases, 32 were due to *Plasmodium vivax*, 21 were due to *Plasmodium falciparum* and 1 case was due to a mixed *P. vivax* and *P. falciparum* infection. Nine of the 54 cases were regarded as severe, having evidence of cerebral involvement or appearing unusually toxic.

"All patients were hospitalized for at least six days and had examinations of thick and thin blood smears for malaria daily for the first six days after starting treatment. Temperatures were taken every four hours during fever and all patients were observed closely for toxic symptoms." Although all patients were requested to return to the outpatient department following hospitalization, only 18 patients returned at least once for physical examination and malaria smears; of these, only 4 were followed for six months or more.

"The first 15 cases were treated with a total dose of chloroquine base 0.015 Gm./pound body weight, divided into 2/5 as initial dose, 1/5 in eight hours and 1/5 on each of the second and third days. The other 39 cases were treated by a schedule according to age (table I). Any dose of medication vomited was immediately repeated. In all cases a three day treatment schedule was used."

"All patients rapidly became asymptomatic and by the fourth day all had negative blood smears except for 5 patients showing sexual forms of *P. falciparum*. The average number of days of parasitemia, excluding *P. falciparum* gametocytes, was 2.1. Maximum duration of fever was five days, average two days. There were no deaths.

"Twenty patients complained of or exhibited listlessness, vertigo, nausea, vomiting or anorexia during treatment. Because malaria classically produces these manifestations, no attempt is made to represent them as evidence of chloroquine toxicity alone. Two children who persistently vomited their medication retained chloroquine introduced by gastric tube. However, of a control group of 16 nonmalarial (tuberculous) children given dosage according to table I, 10 manifested vomiting and anorexia and 1 complained of vertigo and double vision. All retained medication after sedation.

"Four malarial patients tested showed a positive cephalin-cholesterol flocculation reaction. Although this phenomenon is common in malaria, a possible relationship to chloroquine therapy was considered, and the 16 nonmalarial children were noted to have no change in icterus index, van den Bergh reaction or cephalin-cholesterol flocculation reaction four days after starting the chloroquine therapy.

"Six patients had more than one bout of symptomatic malaria." Four patients had recurrences of *P. vivax* malaria two weeks to six months after the first episode. One patient had *P. vivax* malaria two months after leaving the hospital apparently cured of *P. falciparum* malaria. One patient a 42.6 Kg. boy violently ill with *P. falciparum* malaria, was treated for malaria by another physician seven days after cessa-

Table I

Dosage Schedule of Choloroquine Diphosphate by Age

Age	Total Dose*	Dose on Entry	Dose in 8 Hours	Dose on Each of Following 2 Days
6-18 mos.	0.60 Gm.	1 ½ tab.	½ tab.	1 tab.
18 mos.-5 yrs.	0.75 Gm.	2 tab.	1 tab.	1 tab.
5-8 yrs.	0.975 Gm.	3 tab.	1½ tab.	1½ tab.
over 8 yrs.	1.50 Gm.	4 tab.	2 tab.	2 tab.

One tablet of chloroquine diphosphate is 0.25 Gm. and contains 0.15 Gm. chloroquine base.
*Total dose is calculated by wt. of chloroquine base.

tion of the writers' therapy, and is regarded by the writers as a possible treatment failure.

"Four patients showed gametocytes of *P. falciparum* for variable periods (2 to 12 days) after the chloroquine treatment."

Diphtheria Immunisation in Young Babies. A Study of Some Factors Involved—BARR, MOLLIE, GLENNY, A. T. AND RANDALL, K. J.—*Lancet*, 1: 6 (January 7) 1950.

During the past three years the writers have been investigating the quantity and rate of loss of maternally transmitted diphtheria antitoxin in the newborn, how far the passive antitoxin interferes with active response to an injection of prophylactic, and the age at which babies can respond efficiently to active immunisation.

The writers have tested the antitoxic level in the cord blood of each baby, and investigated the level of antitoxin which will interfere with active immunisation by two doses, each of 0.5 ml. of A. P. T. (50 Lf per ml.). "The influence of age on response has also been considered. In some cases the amount of antitoxin remaining in the baby's blood at the time of the first injection was obtained by calculation from the antitoxic level in the cord blood, and in others it was obtained by titrations of a blood sample."

"Effect of Amount of Passively Acquired Antitoxin on Response to Immunisation.—Table I shows the antitoxic levels of babies about two months after the second injection of 0.5 ml. of A. P. T. The results have been grouped according to the amount of passive antitoxin present at the time of the first injection, and one group has been further subdivided according to age. An amount of passive antitoxin less than 0.02 unit per ml. does not interfere with active immunisation under the conditions here present. The 10 babies with titres of 0.01-0.02 unit per ml. responded as well to immunisation as did 31 babies of similar ages but with less passive antitoxin; the geometric means of the titres reached were 0.272 and 0.250 respectively. The logs of the levels attained by all the babies with less than 0.02 unit of passive antitoxin per ml. at the time of the first injection showed a good approximation to a normal distribution ($X^2 = 3.019 - P = 0.397$); and the mean value of 0.265 unit per ml. for the group, about two months after the second injection, is satisfactory. The values recorded in the tables include values up to the next figure given—e.g., 0.2 unit includes values between 0.2 and 0.5 unit. Hence in calculating the geometric means of groups each value has been taken as the geometric means of the limits within which it lay, tests having been made at about 100 per cent differences. Group D, composed of babies with 0.02-0.04 unit of passive antitoxin per ml., is small, but the geometric mean of the values is definitely lower than those of groups A, B, and C, and this is also the case with group E, which had 0.04-0.1 unit per ml. at the time of injection. One baby produced 1 unit per ml., but the values, taken as a whole, were lower, and it seems that in group E the passive antitoxin interfered with the first dose of prophylactic in about half the babies. It is possible that the

Table I. Antitoxic Response of Babies to Two Injections, Each of 0.5 ml. of A.P.T.: Babies Grouped According to the Titre of Passive Antitoxin Present at the Time of the First Injection

Group	Passive antitoxin at time of 1st injection (unit/ml.)	Age (weeks)	No. of babies producing titres (unit/ml.)								Total no.	Geometric mean (unit/ml.)	Av. interval (weeks) between	
			<0.01	0.01	0.02	0.04	0.1	0.2	0.5	1.0			1st and 2nd injections	2nd injection & blood sample
A	Under 0.02	6-13	..	..	..	1	3	11	4	1	20	0.329	8.1	8.9
B		14-26	..	..	..	3	6	9	3	2	23	0.267	8.7	8.5
C		Over 26	..	..	2	3	1	10	1	1	18	0.207	9.6	8.9
A+B+C	Total under 0.02	6 upward	..	..	2	7	10	30	8	4	61	0.265	..	..
D	0.02–0.04	Av. 18.4	..	..	1	2	1	1	2	0	7	0.166	9.9	9.1
E	0.04–0.10	Av. 12.9	..	1	1	1	2	0	0	1	6	0.098	7.8	7.7
F	0.10–0.20	Av. 18.2	3	1	..	1	..	..	..	..	5	<0.020	8.2	8.2

response in these groups was delayed and a slow rise may still have been in progress when the samples of blood were taken. The responses of babies in group F show that the large amount of passive antitoxin present interfered considerably with the start of immunisation.

"Effect of Age. — Consideration of groups A, B, and C suggests that a better response is obtained with babies in the younger age groups. Though the numbers are small, this suggestion is supported by the progressive slight decrease in the mean antitoxic values from A to C and by the greater number of low values (0.02 and 0.05 unit per ml.) in group C. The differences might be accounted for by differences in weight, because the same doses were injected into all the babies and the average weights of group C would be nearly double those of group A. This would lower the effective size of the primary stimulus in two ways: (1) the dose/weight ratio would be lower in the heavier babies; and (2) though the titre of passively conferred antitoxin in units per ml. was the same for all groups, the total amount of this passive antitoxin present in the circulation would be greater in the older and bigger babies. It is thus very probable that the passive antitoxin would interfere with immunisation more in the heavier children. If this is so, the question of large initial doses is of very great importance if immunisation is not done in the first few months of life. There is a further possibility that some degree of poor immunisability might be acquired after the first few months of life.

"In group A, 5 babies received their first injection at the age of 6-8 weeks, and the geometric mean of their antitoxic values after immunisation was 0.314 unit per ml., compared with 0.329 unit per ml. for the whole group. These results show that successful immunisation is possible at a very early age.

"Effect of Interval Between Injections. —Table II shows the antitoxic values of babies injected with two doses of A. P. T., each of 0.5 ml., given at different intervals. The numbers in each group are small, but in babies immunised before the age of 6 months (groups A and B) there is strong evidence that better responses were obtained as the interval between injections was increased. In group C, composed of babies over the age of 6 months, this improvement did not occur. The difference between the age groups, if significant, may again be due to the reduced effect of the primary stimulus, owing to the greater weight and greater total amount of circulating antitoxin in group C. Though, in general, higher values are obtained by increasing the interval between primary and secondary stimulus, this is not the case if the primary stimulus is small."

Table II. Influence on Response of Interval Between Injections of A.P.T. in Babies Whose Passive Antitoxic Levels Were Below 0.02 Unit per ml.

Group (see table I)	Weeks between injections	No. of babies producing titres (unit/ml.)						Total No.	Geometric mean (unit/ml.)
		0.02	0.05	0.1	0.2	0.5	1.0		
A	6, 7	..	1	2	3	..	..	6	0.188
	8	..	..	1	6	3	..	10	0.371
	10-12	..	..	..	2	1	1	4	0.562
B	6, 7	..	2	2	5	..	..	9	0.130
	8, 9	..	1	4	1	2	..	8	0.214
	10-18	..	..	..	3	1	2	6	0.596
C	8, 9	1	1	..	7	1	..	10	0.251
	10-12	1	2	1	3	1	..	8	0.163
Total A, B, and C	6, 7	..	3	4	8	..	..	15	0.189
	8, 9	1	2	5	14	6	..	28	0.269
	10-18	1	2	1	8	3	3	18	0.331

Comparison of Responses of Expectant Mothers and Babies to Immunisation.—Some expectant mothers were Schick tested in the fourth month of pregnancy, and the positive reactors were immunised with two doses, 0.2 and 0.5 ml., of A. P. T. By this means the writers ensured that some babies would be born with large amounts of passive maternally transmitted antitoxin, the rate of loss of which could be followed for a considerable time.

"The scatter of antitoxic values after immunisation of babies in groups A, B, and C in table I is relatively small; 59 out of 61 titres were over 0.04 unit and under 2.0 units per ml. The remaining two levels were between 0.02 and 0.04 unit and were produced by babies in C, the oldest age group. Table III shows how many immunised expectant mothers produced titres falling above, between, or below these limits (over 0.04 unit and under 2.0 units per ml.). The women were divided into those who had been Schick tested and found positive (group L), those not so tested but found to have less than 0.001 unit of antitoxin per ml. in their serum before immunisation (group N), and those with detectable antitoxic levels which ranged from 0.01 to 2.0 units per ml. (group P). In addition to these women there were 2 with high antitoxin levels at the time of their first injection of A. P. T.; 1 had 2-5 units and the other 10-25 units per ml.; neither showed any appreciable rise after immunisation, the recorded values being 3-5 units in the first woman and 12-15 units per ml. in the second. Since all the other expectant mothers in group P produced 6 or more units per ml., it seems that a titre of 2 or more units per ml. may interfere with responses of actively immune persons to the injection of 0.2 ml. of A. P. T., compared with interferences by 0.1 or more unit per ml. in passively immunised babies injected with 0.5 ml. of A. P. T.

"Women with little or no circulating antitoxin, either Schick-positive (L) or with titres below 0.001 unit per ml. (N), appear to fall into three groups: (1) those who give similar results to babies who almost certainly were not actively immune before injection; (2) those who do not respond; and (3) those whose production of antitoxin is considerable and who can be accepted as falling into the category of 'potentially immune without circulating antitoxin.' The antitoxic values reached by these potentially immune women in groups L and N suggest that preliminary Schick testing may have some influence on immunisation, though the numbers involved are very small; 3 out of 4 not Schick tested gave lower values (2, 3, and 5 units per ml.) than those tested, only 2 out of 6 of whom gave titres below 10 (6 and 8) units per ml. Of the others, the remaining untested mother produced 13.5 units per ml., and the 4 other tested mothers produced 15, 30, 30, and 100 units per ml.

"Thus, of 26 adults below the Schick level of immunity, 8 were very poor responders to immunisation, about 9 gave normal responses, and about 9 were potentially immune." It is impossible to decide definitely whether those women producing 2-5 units per ml. were potentially immune or not, though no baby the

Table III. Antitoxic Values Reached by Expectant Mothers and by Babies After Immunisation with A.P.T., the Mothers Having Received Two Doses of 0.2 and 0.5 ml. and the Babies Two Doses Each of 0.5 ml.

Groups	No. of persons reaching (after immunisation) antitoxic titres (units/ml.)							Total
	Under 0.001	0.001-0.01	0.01-0.04	0.04-2.0	2-10	10-100	100 and over	
Babies from table II								
H, under 6 months old	0	0	0	43	0	0	0	43
K, over 6 " "	0	0	2	16	0	0	0	18
Expectant mothers								
L, Schick tested, positive	3	2	0	6	1	3	1	16
N, Not Schick tested; antitoxic titre under 0.001	3	0	0	3	3	1	0	10
P, Not Schick tested; antitoxic titre 0.01-2.0	0	0	0	0	3	6	0	9

writers have yet tested has produced 2 units or more per ml.

"It appears probable that all in group P and those in L and N who were potentially immune would have responded strongly to a single injection of prophylactic; of 3 Schick-positive women whose immunisation was discontinued after the first injection of 0.2 ml., 1 was obviously potentially immune and produced 15 units per ml."

"There was no correlation between the response to immunisation of expectant mothers and of their babies."

"Only one factor has been kept constant in all these experiments on immunisation of babies—i.e., all received two doses of A.P.T., each of 0.5 ml. Any conclusions drawn from the results, regarding optimum interval between injections, or the level of maternally conferred passive antitoxin causing interference with active immunisation, can only be applied to the active immunisation of babies with two doses of 0.5 ml. of A.P.T. This must always be borne in mind because, if the first dose of A.P.T. were 0.3 ml., a lower level of passive antitoxin would bring about interference so that immunisation would have to be delayed for a slightly longer time after birth, and the optimum interval between injections would be shorter. The effect of giving this lower dose is entirely disadvantageous from the immunological standpoint, because the larger the initial dose the longer is the interval which can with advantage be allowed before the second dose, and both these factors bring about the establishment of sound basal immunity. Nor does there seem to be any good reason for injecting young babies with small doses, since reactions are not encountered among them and they do not show any adverse emotional disturbances."

"By calculation from antitoxic values of cord blood it is estimated that over 80 per cent of a population of 200 babies born in South East London could be successfully immunised, starting at the age of 3 months. It is suggested that all babies, except those born of potentially immune mothers further immunised during pregnancy, could be successfully immunised with three injections of prophylactic given at the ages of 3, 6, and 18 months."

"The Schick test should not be used in fundamental work designed to throw light on methods of immunisation. It is insufficiently stringent and does not reveal the scatter of values, which should be small. Its field of usefulness is essentially confined to routine work."

Symposium Section

Cortisone, ACTH and Deoxycortone Therapy

Just one year has passed since, Hench, Kendall and their associates at the Mayo Clinic caused a furor by the announcements of their dramatic successes with cortisone and ACTH. Their results were widely chronicled and illustrated by moving and still pictures. Their own reports in medical journals and at medical assemblies were—in keeping with the growing custom—supplemented by glamorous accounts in the public press and magazines. All of this publicity naturally aroused hope that the solution of a long and discouraging conquest was, at least, at the threshold of success.

We have previously reviewed the work of the Mayo group in this section, but during the past year a considerable amount of literature has accumulated and much more will have appeared before this is off the press. Meanwhile an attempt will be made to collect, correlate and classify the information available. It will be for the purpose of bringing a subject of growing interest up to date, as well as complying with numerous requests for such information. We hope to clarify much of the confusion caused by public press articles, and so assist those who have mailed in many newspaper clippings which have been somewhat confusing to us as they may have been to many others.

* * *

First, let us reiterate what was emphasized in our previous review that this whole approach to the rheumatic problem is not merely a flash in the pan. It was the result of patient research on the physiologic side by Hench and his colleagues and on the biochemical side by Kendall and his colleagues, both at the Mayo Clinic. A review of their work seems very definitely indicated in order to keep the record straight. This is because with a flood of reports from many sources has come implications and claims which are not at all convincing or in accord with the reliable and reputable sources of information upon which we wholly rely for our interpretations in this Digest.

We may start 19 years ago when a chemical and physiologic investigation of the adrenal cortex was undertaken by Dr. Edward C. Kendall and his associates in the biochemical laboratories of the Mayo Foundation for Medical Education and Research, for the purpose of finding compounds which might be useful therapeutically. After a number of years, several compounds were obtained in crystalline form. This made it possible to undertake clinical investigations. These compounds were used by a group from the Division of Biochemistry and the Division of Medicine of the Foundation.

The first of them was the adrenal cortical hormone known in the realms of the biochemists as 17-hydroxy-11-dehydrocorticosterone but known for convenience as compound E Kendall and later cortisone, which led up to the study of two of the hormones about which so much has been written in the past year.

The second is the pituitary adrenocorticotropic hormone for which the alphabetic abbreviation ACTH is used. The therapeutic value of both has been studied rather briefly. These hormones were evolved from the studies of Kendall and his associates in the Biochemical laboratories. Beginning in 1934, four crystalline compounds, designated A,B,C and D, were isolated and in the following year two more, called E and F, were developed. Definite chemical formulas were assigned to these in 1937 and 1938. At about the same time it was shown by Dr. Ingle, who was then working in Dr. Kendall's laboratory at the Foundation, that the compound E had a marked effect on muscular activity. Later it was found to influence carbohydrate metabolism, and other investigators showed that it increased physiologic resistance to stress, cold and

toxic substances such as typhoid vaccine. However, so little of the compound was available that the work had to be confined to experiments on mice and rats. As a consequence progress was slow.

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Just before the beginning of the American involvement in the war, in the fall of 1941, requests were made to the National Research Council by the Army and the Navy medical corps for a large supply of adrenal hormones, because it was alleged that the pilots of the *Luftwaffe* were being injected with an extract of the adrenal cortex which made it possible for them to fly at ease at an altitude of 40,000 feet or more. Whether or not this was true, the Council surveyed 22 laboratories which it was found were engaged in work related to the laboratory production of these hormones. A series of conferences were held in Washington where ideas were exchanged, and investigations started to accelerate the production of these hormones by different methods. A mass of information was accumulated but only two sustained investigations approached results encouraging enough to follow through. One of these was in the laboratories of the Mayo Foundation and the other, in the research laboratories of Merck and Company, Inc. In 1944 the Foundation laboratories made a small amount of dehydrocorticosterone (compound A) but in December, 1945, a larger amount was prepared in the Merck laboratories. This compound was used in an investigation of Addison's disease but was soon discarded as being of no value at all.

This left the compound E Kendall and the pituitary adrenocorticotropic hormone (ACTH) for clinical investigation. So a team composed of Dr. Kendall of the Division of Biochemistry and Dr. Philip S. Hench and his associates of the Division of Medicine of the Foundation started such an investigation. Among those referred to as "associates" must be included the names of Doctors Charles H. Slocumb, Arlie R. Barnes, Harry L. Smith and Howard F. Polley, all of the Mayo Clinic, and Doctors Jacob van de Kamp and Lewis H. Sarett of the research laboratories of Merck and Company. All of these contributed to the team headed by Dr. Hench and Dr. Kendall in the development of what has already been "ranked with insulin as one of the great medical discoveries of our generation." So when the term "associates" is used hereinafter it in no way is intended to disparage the work of these members of the team.

* * *

As a background against which the more recent work with hormones may be viewed, it is desirable to recall that Dr. Hench has been studying the beneficial effects of pregnancy and jaundice on rheumatoid arthritis since 1929. From the results of his many studies and those of others, conclusions were reached which indicated that "while the pathologic anatomy of rheumatoid arthritis is more or less irreversible, the pathologic physiology of the disease is potentially reversible, sometimes dramatically so." In other words, the disturbance in the human physiology could sometimes be controlled dramatically even though the crippling pathology remained as a permanent anatomic defect. Hench believed that this was due to corrective forces which may be dormant within every rheumatoid patient awaiting only the proper stimulation. Upon this belief he based his opinion that this inherent factor influencing the reversibility of rheumatoid arthritis is activated more effectively by the intercurrence of jaundice or pregnancy than it is by any other condition or agent thus far known. So he contends that "regardless of the supposed 'validity' of the microbic theory, rheumatoid arthritis can be profoundly influenced by phenomena which are primarily biochemical." So the problem was to harmonize the long-prevailing microbic theory of the origin of rheumatoid arthritis with the phenomenon of relief of the disease by jaundice or pregnancy. It became easier, rather, to consider that rheumatoid arthritis may represent, not a microbic disease, but some basic biochemical disturbance which is transiently corrected by some incidental biologic change common to a number of apparently unrelated events. So it seemed logical to suppose that what causes relief of rheumatoid arthritis in pregnancy is closely related to, if not

identical with, that which relieves the same disease in jaundice. Hench then reasoned that it could be neither hyperbilirubinemia nor a unisexual (female) hormone since neither of these is common in pregnancy and jaundice. So he believed that the discovery of some biochemical denominator common to various agents or states beneficial in rheumatoid arthritis, but common especially to jaundice and pregnancy, would provide us with an improved treatment or control of the disease.

* * *

Perhaps, it is desirable to pause here and assume that some may be surprised, if not astonished, at what may understandingly be called an extraordinary—and may be bizarre—hypothesis upon which to base an investigation that may lead to the better management of a disease the treatment of which has been so unsatisfactory for so many years. Certainly the microbic theory has never been confirmed. So after all Hench and Kendall and their associates are fully justified in thinking that a new approach is long overdue. Pasteur was not astonished when Ehrlich developed his theory of immunity which led to vaccinotherapy and serotherapy. Moreover, Ehrlich turned to the development of chemotherapy when he realized that both of these forms of therapy had definite limitations. Besides, the physiologic approach to the study of the disease is by no means new. It has long guided internists and surgeons and whenever either have disregarded it, they encountered difficulties. Outstanding examples of the physiologic approach through the endocrines are numerous. Those of which we may think first are insulin and thyroxine. Then we should recall that it was Kendall who first isolated thyroxine from the thyroid in the same laboratory from which he later released glutathione, and now the group of hormones from the suprarenal cortex. It is not surprising then that he and Hench, working together, should be physiologically minded and visualize a biochemical approach in the solution of rheumatic diseases which so far have yielded to no other. Naturally, the earlier investigations were devoted to attempts to reproduce the effects of jaundice and pregnancy. The Mayo group and others to whom they give full credit used, more or less empirically, many agents and measures, some related to jaundice, some to pregnancy. These included the transfusion of blood from jaundiced or pregnant donors, the administration of female hormones and various biliary products, the production of experimental bilirubinemia, icterogenic serum and other similar procedures. The results generally were unsatisfactory.

* * *

Quite a different line of physiologic approach to the genesis of diseases in general has arisen from the research of Hans Selye and his colleagues at the Institute of Experimental Medicine and Surgery at the University of Montreal, Canada. It, too, must be called extraordinary—and even bizarre—as we did in outlining the physiologic and chemical studies of Hench, Kendall and associates. But words of astonishment, elevated eyebrows and the stroking of chins greeted the departures from the conventional by Pasteur, Lister and Ehrlich. What was said, written and thought of these medical masters before their ideas were clearly understood by the rank and file was what might be called an antipodal antithesis when compared to the reverence accorded them in inscriptions on stone and bronze all over the world today. It took many years before the full significance of their ideas of approaching diseases was appreciated. For example, it has been just a little more than a decade since we have been able to possess chemotherapeutic agents in such abundance, although Ehrlich visualized them more than 50 years ago.

So let it be learned from the past that if revolutionary changes are met without prejudice and with an open mind, their advantages and shortcomings will be understood sooner than if they are met with a smoke screen of derision to obscure inability to comprehend. Of even greater importance, they should never be discredited by those who take advantage of the opportunity to seek personal aggrandizement or profit by trying to "steal the show" or by exploiting newer and better "wonder drugs." If the radical changes are

wrong, they will soon be abandoned by all honest men of science.

So, as the conception of Hans Selye and his colleagues is closely related to the hypothesis of Hench, Kendall and their associates, it must be included in any review of the newer ideas concerning rheumatic diseases. Selye has called his conception of disease genesis "The General Adaptation Syndrome" and he refers to the diseases resulting from it as "diseases of adaptation." He reports that his experimental and clinical observations have shown that, in addition to the specific adaptive reactions (e.g., serologic reactions to specific antigens, muscular hypertrophy subsequent to physical work, proliferation of the epidermis where the skin is exposed to pressure or friction), there are certain physiologic mechanisms which help to raise resistance to damage as such. The endocrine system plays a prominent part in these latter reactions, which occur irrespective of the specific nature of the evocative damaging agent. He then maintains that the sum of all those nonspecific, systemic reactions of the body which ensue upon long-continued exposure to stress has been termed the "general adaptation syndrome." It is characterized by a number of morphologic and functional changes. Among the most prominent of these are: enlargement of the adrenal cortex with increased corticoid-hormone secretion, involution of the thymus and of other lymphatic organs, gastrointestinal ulcers, certain metabolic changes and variations in the resistance of the organism. Selye contends that if an individual is continuously exposed to stress, the resulting general adaptation syndrome evolves in three distinct stages:

1. The *alarm reaction*, which is defined as the sum of all nonspecific systemic phenomena due to sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted. Some of these phenomena are only passive and represent signs of damage or "shock," e.g., hypothermia, hypotension, hemoconcentration, increased capillary permeability, hypochloremia, depression of the nervous system; others are manifestations of active defense against shock, e.g., corticoadrenal enlargement, increased corticotrophin and corticoid production, hyperchloremia. If the causal stress is of medium intensity, the alarm reaction tends to evolve in two distinct phases, the phenomena of shock being followed by those of countershock. However, in most cases the manifestations of shock and defense are intermixed; indeed the sequence of events may even be reversed, e.g., in case of progressively increasing fatal stress. Here some countershock develops first, when the body can still resist, but subsequently shock manifestations become increasingly more prominent as the augmenting intensity of the stress makes further resistance impossible.

2. The *stage of resistance* is defined as the sum of all nonspecific systemic reactions caused by prolonged exposure to stimuli to which the organism has acquired adaptation. It is essentially a "protracted countershock." Resistance is increased to the particular agent to which the body has been exposed, and this is usually accompanied by marked decrease in resistance to other types of stress. The impression is gained that during the stage of resistance, adaptation to one agent is acquired "at the expense of" resistance to other agents.

3. The *stage of exhaustion* represents the sum of all nonspecific systemic reactions which ultimately develop as the result of prolonged exposure to stimuli to which adaptation had been developed, but could no longer be maintained.

Selye has introduced many schematic charts and graphs to explain his general adaptation syndrome which it is not feasible to reproduce in so brief a presentation of his theories.

Selye suggests that some of the most important diseases related to the by-products of the endocrine reactions are hypertension and "hypertensive diseases," nephrosclerosis, rheumatic diseases and many other secondary diseases due to excessive or abnormal response to stress. These maladies are, therefore, believed to be "diseases of adaptation" because they result from abnormal adaptative reactions to stress.

Paradoxic as it may seem, Selye has also shown that products derived from the adrenal cortex have participated in the pathogenesis of arthritis in experimental animals. He emphasizes that much more work will be required to elucidate the complexities of the diseases of adaptation.

Meanwhile, Selye's "general adaptation syndrome" and the theories of Hench and Kendall comprise the background against which hormone therapy of rheumatic diseases must be viewed.

* * *

In any event when the biochemical laboratories at the Mayo Foundation and the Merck laboratory produced enough cortisone to start a clinical study, 14 patients with rheumatoid arthritis were given 100 mg. of it after all previous analgesic agents, physical therapy and other treatment were discontinued.

The factor of "hospitalization" (rest in bed, psychotherapy) was unavoidable, but except as they were disabled the patients were ambulatory, and when improved were encouraged to assume as much activity as convenient inside and outside the hospital as walking and shopping downtown. One patient, a local physician, eventually was given cortisone as an outpatient after he returned to work. Within a few days muscular and articular stiffness began to diminish, often within the first 48 hours, and often very markedly or completely relieved within a few days. Next, articular tenderness and pain on motion were lessened. Then articular swellings generally diminished, sometimes fairly rapidly and completely, occasionally slowly and incompletely. In one article an impressive sequence of photographs of a patient's hands illustrates the rapid improvement. In 3 cases mild flexion deformities of knees and elbows disappeared within 7 to 10 days. Patients previously unable to get out of bed unassisted, to rise from chairs or toilets, shave, wash the hair or back of the neck, open doors with one hand, wring a wash cloth, lift a cup or book and climb stairs, resumed such activities without assistance within a few days after beginning treatment. In addition to still photographs to illustrate the improvement in deformities, the rapid restoration of ability to use previously stiff joints and the resumption of the listed activities were recorded in motion pictures. Then because this hormone acts like insulin, the return of the symptoms after it was withdrawn was later recorded in subsequent motion pictures for comparison. Weight gains were the usual sequence after treatment.

The laboratory studies revealed a consistent decrease in sedimentation rates which was immediate or slightly delayed, increase in hemoglobin from 1.4 to 2 Gm. per 100 cc., increase in erythrocytes by 500,000 to 1,000,000 cells per cu. mm. within a few weeks. Generally, the patients expressed a feeling of well-being and as the physician patient expressed his relief: "When I take the injection I lose completely my most distressing symptom, 'toxicity'; also all of my fibrositis and most but not all of my arthritis. All I have left is arthritis in miniature." These were the patients of whom moving and still pictures have been widely circulated.

* * *

Obviously the number of cases of rheumatoid arthritis and 3 cases of rheumatic fever in which Hench and his associates used cortisone were too few to warrant any conclusive appraisal. This was clearly implied by Hench when he suggested that it was merely an "investigation." In any event, the spectacular results were confirmed by others with whom the small supply was shared.

They were Dr. W. Paul Holbrook of Tucson, Arizona, president of the Arthritis and Rheumatism Foundation; Dr. Bauer of Harvard; Dr. Richard H. Freyberg of Cornell University Medical College; Dr. Edward Rosenberg of Michael Reese Hospital, president and vice president of the American Rheumatism Association, and Dr. Edward Boland of the University of California Medical School. Each of these contributors to the problem of rheumatism has used cortisone in 1 or 2 patients with excellent results. Dr. Boland said a patient who was bedridden walked and fed herself within 48 hours of starting treatment and "after nine days of treatment she literally danced a jig."

Dr. Hench was given a great ovation at the International Congress on Rheumatic Disease which was held in New York City in the early part of June, 1949, and the consensus at this international meeting was that it was "a wonderful thing to hear of and see (moving pictures) the

effects produced in a few hours in apparently completely crippled patients.

When Dr. Hench and Dr. Kendall appeared last month at the meeting of the American College of Physicians at Boston, the tendency to exult was restrained by the desire to obtain authoritative answers from these two conservative men of science who have never left any doubt in our minds that they considered what they had accomplished was still an "investigation." This desire was the result of the panicky impulse to take advantage of this entirely different conception of rheumatoid arthritis which has been paralleled only by the comparatively recent announcement that the common cold might be eliminated by introducing antihistaminics into the conventional tablets of aspirin, caffeine, etc. This impulse was relieved in many ways. The discovery of Hench and Kendall created grist for a wide variety of literary mills. The conservative reports of those to whom a small share of the very scarce material was made available was soon eclipsed by an astonishing number of reports of the use of cortisone, ACTH and alleged equivalents—even facsimiles—in a long list of diseases. Naturally this created an impression among the dependent medical profession in bulk that the original announcement of the scarcity of hormones was a gross overstatement. Articles appeared in reputable journals and in those less reputable, in Bulletins of less well known clinics and groups, in house organs and advertising material of drug houses, either unknown or those who have shaken medical confidence before, but the most dramatic and glamorous stories were in newspapers and magazines. In these they were extolled as initiating the "era of the hormones" and, as one of the reputable science writers suggested, they not only may influence "arthritis and heart disease" but their usefulness may extend "from gout to asthma to dementia praecox." So, after reading the articles which have appeared up to the present writing, we believe that it would be much easier to list the disease states in which these two hormones and their alleged substitutes have not been used, than to enumerate those in which they have been reported to be more or less effective. This and so much more had confused so many that those in the well filled Mechanics Hall in Boston were anxious to get the many answers from Dr. Hench and Dr. Kendall.

They got what they went there to hear. Moreover, it was clear to all present that both of these reputable and conservative scientists had been very much annoyed by the activities of elements within and without the medical profession who more and more never overlook an opportunity to "crash the headlines" or seek financial gain from a public from whom untold millions of dollars are being fraudulently obtained in the sale of "wonder drugs."

It is understandable why enthusiasm got out of bounds. Hormone therapy attracted all kinds of interest even though at the time Merck and Company, who collaborated with Hench and Kendall, clearly stated that the production of cortisone presented a most complicated problem. At the time its synthesis had been partially developed but the steps necessary are numerous and each contribute toward extending the production time.

The extraction of hormones from the adrenal cortex is, of course, not new as evidenced by the commonly used adrenalin extract in the form of chloride; cortin, a deficiency of which results in the syndrome called Addison's disease; cortiode, a proprietary offered for hypertension, angina pectoris and coronary sclerosis; cortigen, a commercial adrenal extract claimed to contain the life-sustaining principles of the adrenal cortex; cortisupren, another "life sustainer"—and others which are still being offered by newspaper and other advertising. So it becomes apparent that the adrenal cortex has been a fascinating field which has attracted all kinds of investigators.

Any detailed discussion of the production of cortisone from the adrenal cortex is beyond the scope of this review, but it may be appropriate to call attention to the basic information that years ago chemists found in certain animal and vegetable fats an unsaponifiable material. This material was insoluble in water and could not be made into a soap by boiling with an alkali. Eventually these compounds were called steroids, and it was learned that they are far more complex in structure than the fats. They contain carbon, oxygen and hydrogen and are soluble in

most of the organic solvents. They contain what is termed the cyclopentenophenanthrene ring, which can be regarded as a condensed carbon-ring structure.

The steroids from the adrenal cortex are numerous and we will refrain from saying how many. Suffice it to say that at least, the partial synthesis of cortisone and the separation of larger amounts of ACTH from the pituitary glands of animals, a herculean task, has been accomplished in a short time, so that adequate amounts of both materials became available for trial in many diseases of human beings. This has opened new vistas for research which has attracted attention all over the world. These we will not list for the present, but it is our impression that what Hench, Kendall and Selye have started shows definite signs of a new approach to the conquest of human diseases which may be quite as epochal as those initiated by Pasteur, Lister and Ehrlich.

Late in 1949 Lewin and Wassén called attention to the fact that two Swedish workers showed that implantation of calf hypophysis in a case of severe rheumatoid arthritis caused the disease to take a more favorable course. Lewin believed that some material similar to that which Hench had used in rheumatoid arthritis would have a beneficial effect if used on patients with this condition. He selected deoxycortone (desoxycorticosterone) acetate in 1 ml. of oleum arachis, immediately followed by an intravenous injection of 1 Gm. of ascorbic acid (10 ml. of 10 per cent solution). Five minutes after the injections the articular pain began to diminish and the articular mobility began to increase. Fifteen to 30 minutes later, the pain had practically disappeared and the mobility improved as much as the anatomic changes in the joints and muscular atrophy would allow. All the patients reacted in a similar way. In some cases the improvement was astounding. One of the patients was completely crippled by pain and contractures after rheumatoid arthritis for 15 years; after one combined injection, she sat up with ease and moved her arms and legs about freely; all her pain had gone. It was noted that the skin became warmer and redder in the articular regions after the injection. Some patients became greatly exhilarated after the injections—more than one would expect from the mere relief of pain.

The effect lasted from two to six hours, occasionally more than 24 hours. It seems as though it lasts longer with each further injection. In more acute cases one or two injections have been enough to banish the pain for two or three weeks.

This drug which has been available for some time has been used extensively in England, and in any issue of the *Lancet* in the latter part of 1949 and so far in 1950 letters have appeared extolling its virtues or expressing disappointment. While there has been some variation in the use of this drug, Lewin and Wassén suggest that the doses should not exceed 5 mg. of desoxycorticosterone acetate and/or 1 Gm. of ascorbic acid. On the other hand, half these amounts seems to be equally effective. The ascorbic acid can also be given intramuscularly, but no effect has been observed after oral administration.

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So an attempt has been made to collect, correlate and classify the information available at this time in the voluminous and growing literature on cortisone, ACTH and deoxycortone. The original conditions comprising the rheumatic diseases have very nearly been pushed into second place through the use of these hormones in other conditions. As in other highly publicized drugs there has appeared on the market a number of preparations supposed to be derived from the adrenal cortex or pituitary gland. Their merits have been extolled by elaborate advertising and detail men. They bear trade names simulating the original names. Of their merits we know nothing. But we cannot suppress the belief that a conservative attitude be assumed in using them. We think with Spies that these hormones are "a tool for clinical and laboratory research." It is agreed that much more study is necessary. Meanwhile they should be used discriminately.

They are not without deleterious effects. For example, there have been reports that the use of desoxycorticosterone acetate has actually caused subacute arthritis with fever and increased sedimentation rate. It has been used in Addison's disease and is

known that it has a powerful sodium-retaining effect and can cause water retention to the point of edema, hydremia and death. Attention has been called to Selye's experimental production of arthritis in animals by the administration of this material. It has produced glycosuria, and Thorn and his associates and Boland and Headly have noted a greatly increased requirement for insulin in diabetic patients receiving cortisone. Others have confirmed this. Quite recently undesirable effects at the Mayo Clinic included Cushing's syndrome characterized by rounding of the facial contour (moon face), acne keratosis pilaris, muscular weakness, edema, amenorrhea, purplish cutaneous striations, impairment of carbohydrate tolerance, negative nitrogen balance and hypopotassemic alkalosis. Thus we could continue to cite reasons why these drugs should be used with caution.

So far the work of Hench, Kendall and associates, and especially that of Selye, may prove to be a revolutionary change in our approach to human diseases. Time will tell. Meanwhile, what appears to be something out of the ordinary and which seems to possess potentialities should not be discredited by indiscrimination and erratic exploitation.

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Electrophrenic Respiration

Artificial respiration can be given either by manual manipulation of the patient, by intermittent positive pressure or by an "iron lung." Recently Sarnhoff and his co-workers have developed a new method which depends on intermittent stimulation of the phrenic nerve. In experiments on cats and dogs the nerve was exposed and a silver electrode applied, an indifferent electrode being placed anywhere on the skin. A Grass stimulator supplied faradic stimuli at a rate of 40 per minute. The current was fed through a rotating potentiometer which in the course of each respiratory cycle gradually increased the voltage to three volts and then gradually reduced it. This stimulus gives a slow contraction of the diaphragm resembling the normal movement. When the animals were anesthetized to the point of respiratory arrest, stimulation of one phrenic nerve was sufficient to maintain a normal tidal air and normal arterial oxygen and carbon dioxide tensions. The tidal air could be regulated by reducing the peak voltage.

The method was tested in a patient whose phrenic nerve was crushed for severe chronic diaphragmatic flutter, an electrode being left on the right phrenic nerve. After operation, when the patient was conscious, the effect of artificial respiration by rhythmic stimulation of the right phrenic nerve was investigated. Spontaneous respiratory movements stopped during periods of stimulation but the amount of air breathed each minute and the tidal air remained unchanged or even increased in volume. Although the ventilation of the left lung depended largely on the movements of the right diaphragm, there was no fall in arterial oxygen saturation; in fact oximeter studies showed an increase in arterial saturation during electrophrenic respiration. The electrode was left in place for five days before removal, during which time spontaneous diaphragmatic movements between periods of stimulation showed no reduction in amplitude. This was taken to indicate that there was no damage to the phrenic nerve by the stimulating electrode. Although the patient did not complain of pain and was able to sleep during electrophrenic respiration, he admitted, when closely questioned, that he had some discomfort in the right shoulder while the nerve was being stimulated. This new method of artificial respiration has the great advantage that the apparatus is less cumbersome than the iron lung.

Cold in Cardiac Pain

Nearly all sufferers from cardiac pain of effort find that there is no surer way of bringing on pain than walking out in a cold wind after a meal. An effort test has been applied quite often in studying this type of pain and the effect of exertion on the cardiogram in cases where the diagnosis is in doubt, but the experimental application of cold seems to be used only in the rather controversial "cold-pressor" test for latent hypertension. Berman and McGuire have applied blocks of ice to various parts of the skin in 20 patients with cardiac pain of effort and 20 normal controls. In 3 of the cardiac cases this produced a depression of the S-T segment of 1 mm. in one or more limb leads. In one of these there was a greater depression of S-T when ice was applied to the nose than when it was applied to the forearm. Chest pain without cardiographic change was noted in 3 patients during or soon after the cold application. The controls showed some lowering of the T waves, and since the S-T intervals are not mentioned these were presumably unaffected. However, some normal people have a depressed S-T segment and an inverted T wave after

exercise, and the sum of the depressions in all leads has been taken by some observers as a criterion of abnormality. There is also said to be a difference in the shape of the S-T depression between patients with cardiac ischemia and normal people after exercise. More observations on the cold test in cardiac pain and in normal controls are needed to show whether it can be useful.

Deaths Under 20 Years of Age

In a statistical study of mortality rates in the past decade in New York City, Leona Baumgartner and Vivian Pessin found that the rates among children there, as elsewhere in the country, are on the decline. But in their study from the Department of Health, New York Hospital, and the Department of Pediatrics, Cornell University Medical School, they found that in the same 10 years the mortality rate for persons under 20 years declined less rapidly than in previous decades. Nevertheless, the application of new and well recognized procedures in the prevention of deaths due to pneumonia, influenza, appendicitis, diarrhea and contagious diseases, and tuberculosis has led to striking reductions in deaths due to these causes. Because of these reductions, other causes of deaths have assumed new importance. Thus, in children over 1 year of age accidents are today the leading cause of death. Heart disease, tuberculosis and cancer claim a high percentage among those from 10 to 20, while contagious and respiratory diseases are still important in children under 10 years of age.

In infants, the deaths occurring before, at or near birth are of chief importance, with those associated with premature birth assuming an importance that demands active and immediate attention. Despite the gains made, deaths associated with childbirth (i.e., fetal and neonatal deaths) stand second today in claiming lives of all ages in New York City. Only heart disease has a larger mortality. The time has come, these authors believe, for physicians to take cognizance of these facts and to see that all mothers and babies get the kind of care which good pediatricians and obstetricians know can be given. In addition, there is a pressing need for an intensified research program to the end that deaths in infancy and those due to accidents and heart disease can be more effectively prevented.